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(54) Title: POLYPEPTIDES, COMPRISING IL-6 LIGAND-BINDING RECEPTOR DOMAINS AND RELATED NUCLEIC ACIDS, ANTIBODIES, COMPOSITIONS, AND METHODS OF USE

(57) Abstract: The present invention provides, among other things, a polypeptide, and a pharmaceutically acceptable salt thereof, that inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions, a nucleic acid that encodes such a polypeptide and can be expressed in a cell, a nucleic acid that comprises or encodes an antisense nucleic acid molecule or a ribozyme that is specific for such a polypeptide, an antibody that is specific to such a polypeptide, and anti-antibody thereto, a composition comprising such a polypeptide, nucleic acid, antibody or an anti-body and a carrier therefor, a composition comprising a solid support matrix to which is attached an above-described polypeptide or an anti-antibody to a specified polypeptide sequence, a method of prophylactically or therapeutically inhibiting IL-6 signaling in a mammal in need thereof, a mammal in need thereof, and a method of removing IL-6 ligand from a body fluid of an animal.

POLYPEPTIDES COMPRISING IL-6 LIGAND-BINDING RECEPTOR DOMAINS AND RELATED NUCLEIC ACIDS, ANTIBODIES, COMPOSITIONS, AND METHODS OF USE

TECHNICAL FIELD OF THE INVENTION

The present invention relates to polypeptides comprising IL-6 ligand-binding receptor domains, nucleic acids encoding such polypeptides, antibodies, compositions comprising such polypeptides, nucleic acids, or antibodies, and methods of use.

BACKGROUND OF THE INVENTION

Interleukin-6 (IL-6) is a cytokine that is produced in response to various stimulators and is responsible for a variety of biological activities, including the stimulation of B- and T-cell growth and differentiation (Muraguchi et al., *J. Exp. Med.* 167: 332 (1988)), production of acute-phase proteins in response to inflammation or tissue injury (Gauldie et al., *PNAS USA* 84: 7251 (1987); Geiger et al., *Eur. J. Immunol.* 18: 717 (1988)), multilineage hematopoiesis, osteoclast formation, maturation of megakaryocytes, and platelet production. These biological activities are initiated when IL-6 binds to the extracellular portion of the interleukin-6 receptor, which is variously referred to as the interleukin-6 α subunit (IL-6Rα) or B-cell stimulating factor receptor (BSF-2 receptor). When IL-6 binds to IL-6Rα, a complex is formed. The complex then binds to the extracellular portion of the interleukin-6 receptor known as gp130, which is also referred to as the

interleukin-6β subunit (IL-6Rβ). The resulting complex then transmits the IL-6 signal intracellularly.

The precursor of the IL-6 receptor reportedly comprises 468 amino acids (Yamasaki et al., *Science* 241: 825-828 (1988)). The mature IL-6 receptor reportedly comprises 449 amino acids (Yamasaki et al. (1988), *supra*).

Abnormal expression of IL-6 has been implicated in the pathogenesis of a variety of diseases, including multiple myeloma, plasmacytoma, hematological diseases such as plasma cell dyscrasias, leukemia and lymphoma (including non-Hodgkins's lymphoma and Lennert's T-cell lymphoma (Kishimoto, *Blood* 74: 1 (1989)), mesangial proliferative glomerulonephritis, polyclonal B-cell activation conditions, allergic diseases (Type I-IV), rheumatoid arthritis (Hirano et al., *Eur. J. Immunol.* 18: 1797 (1988)), diabetes, multiple sclerosis, SLE, septic shock, bacterial infection, viral infection, post-menopausal osteoporosis, chronic immune deficiency and autoimmune diseases (*Med. Immunol.* 15: 195-201 (1988)), including organ-specific and systemic diseases and AIDS, inflammatory diseases, and Cattleman's disease. In addition, IL-6 production has been associated with cardiac myxoma and cervical cancer (Kishimoto et al., *Ann. Rev. Immunol.* 6: 485 (1988)) *in vivo* and myelomas, histiocytomas and promyelocytic leukemia (Taga et al., *J. Exp. Med.* 166: 967 (1987)) *in vitro*. Attempts to abrogate the effects of abnormal expression of IL-6 can be made at its site of production or at its target.

In view of the above, there remains a need for materials and methods for identifying and designing

agents that inhibit IL-signaling and for treating diseases involving IL-6 signaling prophylactically and therapeutically. It is an object of the present invention to provide such materials and methods. This and other objects and advantages, as well as additional inventive features, will become apparent from the detailed description provided herein.

BRIEF SUMMARY OF THE INVENTION

The present invention provides, among other things, a polypeptide, and a pharmaceutically acceptable salt thereof, that inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions. In one embodiment, the polypeptide has the formula $R^1R^*R^*L^*L^*L^*R^*R^2$, and pharmaceutically acceptable salts thereof, in which R^1 is hydrogen, $R^3C(O)-$ or R^3, and does not comprise an amino acid residue sequence that is identical to an amino acid residue sequence of the α-chain of the IL-6 receptor and is not linked to the moiety $-R^*R^*L^*L^*L^*R^*$ via a glycinyl residue or via a proprionyl residue, R^2 is hydrogen, a polypeptide of from 1 to about 100 amino acid residues, NHR^3 or R^3, and R^3 is a pharmaceutically acceptable substituent group.

In another embodiment, the polypeptide has the formula $R^{10}R^{11}XVL^{*2}L^{*2}VR^{12}$, in which R^{10} and R^{12}, independently, are pharmaceutically acceptable substituents, R^{11} is a naturally-occurring or synthetic amino acid residue that has an acidic or neutral side-chain under physiological conditions, X is any naturally-occurring or synthetic amino acid residue, and L^{*2} is leucinyl or isoleucinyl.

In yet another embodiment, the polypeptide has the formula $R^{20}R^{21}L^*R^*Y^*R^*A^*E^*R^*S^*R^{22}$, in which R^{20} and R^{22} are pharmaceutically acceptable substituents, R^{21} is a naturally-occurring or synthetic amino acid residue that has a basic or neutral side-chain under physiological conditions, L^*, Y^*, E^* and S^* are independently any naturally-occurring or synthetic amino acid residue, R^* is a naturally-occurring or synthetic amino acid residue that has a basic side-chain under physiological conditions, and A^* is alaninyl, glycinyl, isoleucinyl, leucinyl, valinyl, norleucinyl, norvalinyl, sarcosinyl, β-alaninyl or α-aminoisobutyryl.

In still yet another embodiment, the polypeptide comprises at least $I^*A^*I^*V^*L^*R^*F^*$ but less than about 200 amino acid residues that have a sequence that is identical to an amino acid sequence of the α-chain of the IL-6 receptor, in which I^*, L^*, and V^* are independently a naturally-occurring or synthetic amino acid residue having a side-chain consisting of a C_1-C_6 straight chain or C_1-C_6 branched alkyl moiety, R^* is a naturally-occurring or synthetic amino acid residue that has a basic side-chain under physiological conditions, A^* is alaninyl, glycinyl, isoleucinyl, leucinyl, valinyl, norleucinyl, norvalinyl, sarcosinyl, β-alaninyl or α-aminoisobutyryl, and F^* is tyrosinyl, phenylalaninyl, tryptophanyl or α-aminoisobutyryl, with the proviso that at least four of the seven substituents of $I^*A^*I^*V^*L^*R^*F^*$ are selected such that I^* is isoleucinyl, A^* is alaninyl, V^* is valinyl, L^* is leucinyl, R^* is argininyl, and F^* is phenylalaninyl.

In a further embodiment, the polypeptide comprises up to 200 amino acid residues that are identical to an amino acid residue sequence of the β-chain of the IL-6 receptor and comprises the sequence SVIILKYNIQY, TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL, QLPVDVQNGFIRNYTIFYRTIIGN, or IVVPVCLAFLLTTLLGVLFCFNKRDLIKKHIWPNVPDPSKSHIA, any one of which can comprise from one to about six conservative or neutral replacements. The polypeptide can further comprise a pharmaceutically acceptable substituent.

Also provided by the present invention is a nucleic acid that encodes an above-described polypeptide, wherein the polypeptide preferably consists of naturally-occurring amino acid residues. The nucleic acid encoding the polypeptide can be expressed in a cell. The nucleic acid encoding the polypeptide can be operably linked to a signal sequence that causes secretion of at least the polypeptide by a cell in which the nucleic acid is expressed. Alternatively, the nucleic acid comprises or encodes an antisense nucleic acid molecule or a ribozyme that is specific for a nucleotide sequence in a nucleic acid encoding the specified amino acid sequence in an above-described polypeptide.

Further provided by the present invention is a composition comprising an above-described polypeptide or nucleic acid and a carrier therefor. Another composition provided by the present invention is a composition comprising an antibody to an above-described polypeptide, an anti-antibody to an above-described polypeptide, or a solid support matrix to which is attached an above-described polypeptide or an anti-antibody to the

polypeptide sequence RRLLLR, RXVLLV, LRYRAERS, IAIVLRF, SVIILKYNIQY, PSIKSVIILKYNIQY, or a portion of any of the following polypeptides: WTNPSIKSVIILKYNIQY, KLTWTNPSIKSVIILKYNIQY, TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL, QLPVDVQNGFIRNYTIFYRTIIGN, and IVVPVCLAFLLTTLLGVLFCFNKRDLIKKHIWPNVPDPSKSHIA.

Also provided by the present invention is a method of prophylactically or therapeutically inhibiting IL-6 signaling in a mammal. The method comprises administering to a mammal in need thereof an IL-6 signaling inhibiting effective amount of an above-described polypeptide, a nucleic acid encoding such a polypeptide or an antibody to such a polypeptide.

In addition, the present invention provides a method of removing IL-6 ligand from a bodily fluid of an animal. The method comprises extracorporeally contacting the bodily fluid of the animal with a solid-support matrix to which is attached an above-described polypeptide or an anti-antibody to the polypeptide sequence RRLLLR, RXVLLV, LRYRAERS, IAIVLRF, SVIILKYNIQY, PSIKSVIILKYNIQY, or a portion of any of the following polypeptides: WTNPSIKSVIILKYNIQY, KLTWTNPSIKSVIILKYNIQY, TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL, QLPVDVQNGFIRNYTIFYRTIIGN, and IVVPVCLAFLLTTLLGVLFCFNKRDLIKKHIWPNVPDPSKSHIA. Alternatively, the bodily fluid can be contacted with the polypeptide or anti-antibody in solution and then the solution can be contacted with a solid support matrix to which is attached a means to remove the polypeptide or

anti-antibody to which is bound IL-6 ligand from the bodily fluid.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 depicts a listing of synthetic amino acids available (from Bachem, King of Prussia, PA) for incorporation into polypeptides and compounds of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides, among other things, a polypeptide that inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions. The present invention is predicated in part on a detailed study of a series of synthetic polypeptides having the same or similar amino acid sequence as that of IL-6 receptor, in which the ability of each synthetic polypeptide to bind to the IL-6 ligand was measured first in a high-throughput *in vitro* assay, and then confirmed (for at least a subpopulation of the synthetic polypeptides of greater interest) by measuring the ability of the synthetic peptide to inhibit the growth, replication, and survival of IL-6-dependent cells grown in a cellular growth medium comprising IL-6 ligand. Those of skill in the art will recognize that the ability of any particular polypeptide to inhibit IL-6 signaling or function *in vivo* can be easily and rapidly determined using either the techniques employed in the examples provided below, or by using another suitable testing technique, such as the B9 cell growth and signal transduction assays known in the art (*see*, e.g., Halimi

et al., *Eur.Cytokine Netw.* 6: 135-43 (1995)). The skilled artisan would expect the results of such *in vitro* assays to be reasonably predictive of *in vivo* utility.

While not intending to be bound by any particular theory, it is believed that the present inventive polypeptide, and compositions comprising the same, inhibit the ability of IL-6 ligand to bind to the soluble IL-6 receptor or the membrane-bound IL-6 receptor, by binding to unbound IL-6 ligand with sufficient affinity to interfere competitively with IL-6 signaling, IL-6-dependent cellular responses (including changes in one or more of the group consisting of cellular metabolism, cellular growth, cellular replication, and cellular survival; the term "cellular metabolism" includes the ability of the cell to affect neighboring cells by secretion of biomolecules (e.g., paracrines, or exocrines), and/or display of cell-surface biomolecules (e.g., proteins or lipids)).

In each embodiment provided herein, a letter indicates the standard amino acid designated by that letter, and a letter followed directly by an asterisk (*) preferably represents the amino acid represented by the letter (e.g., N represents asparaginyl and T represents threoninyl), or a synthetic or naturally-occurring conservative or neutral substitution therefor, unless otherwise specified. Additionally, in accordance with convention, all amino acid sequences provided herein are given from left to right, such that the first amino acid is amino-terminal and the last is carboxyl-terminal. The synthesis of polypeptides, whether synthetic (i.e., chemical) or biological, is within the skill in the art.

It is within the skill of the ordinary artisan to select synthetic and naturally-occurring amino acids that effect conservative or neutral substitutions for any particular naturally-occurring amino acids. The skilled artisan desirably will consider the context in which any particular amino acid substitution is made, in addition to considering the hydrophobicity or polarity of the side-chain, the general size of the side chain and the pK value of side-chains with acidic or basic character under physiological conditions. For example, lysine, arginine, and histidine are often suitably substituted for each other, and more often arginine and histidine. As is known in the art, this is because all three amino acids have basic side chains, whereas the pK value for the side-chains of lysine and arginine are much closer to each other (about 10 and 12) than to histidine (about 6). Similarly, glycine, alanine, valine, leucine, and isoleucine are often suitably substituted for each other, with the proviso that glycine is frequently not suitably substituted for the other members of the group. This is because each of these amino acids are relatively hydrophobic when incorporated into a polypeptide, but glycine's lack of an α-carbon allows the phi and psi angles of rotation (around the α-carbon) so much conformational freedom that glycinyl residues can trigger changes in conformation or secondary structure that do not often occur when the other amino acids are substituted for each other. Other groups of amino acids frequently suitably substituted for each other include, but are not limited to, the group consisting of glutamic and aspartic acids; the group consisting of

phenylalanine, tyrosine and tryptophan; and the group consisting of serine, threonine and, optionally, tyrosine. Additionally, the skilled artisan can readily group synthetic amino acids with naturally-occurring amino acids.

In the context of the present invention, a polypeptide is "substantially identical" to another polypeptide if it comprises at least about 80% identical amino acids. Desirably, at least about 50% of the non-identical amino acids are conservative or neutral substitutions. Also, desirably, the polypeptides do not differ in length (i.e., due to deletion mutations) by more than about 10%.

In a first embodiment, the present invention provides a polypeptide of the formula $R^1R^*R^*L^*L^*L^*R^*R^2$ (domain I), and pharmaceutically acceptable salts thereof. In this embodiment, R^1 is selected from the group consisting of hydrogen, $R^3C(O)$-, and R^3. However, R^1 does not comprise an amino acid residue sequence that is identical to an amino acid residue sequence of the α—chain of the IL-6 receptor and is not linked to the moiety $-R^*R^*L^*L^*L^*R^*$ via a glycinyl residue or a proprionyl residue. Preferably, R^1 is not linked to the moiety $—R^*R^*L^*L^*L^*R^*$ via either a glycinyl, proprionyl, butyryl, or alaninyl residue, and, more preferably, R^1 does not comprise an amino acid residue sequence that is greater than 50% identical to the amino acid residue sequence RWAGM- at the site of linkage to the moiety $-R^*R^*L^*L^*L^*R^*$.

R^* is independently selected from the group consisting of argininyl, naturally-occurring argininyl equivalents, and synthetic argininyl equivalents.

L^* is independently selected from the group consisting of leucinyl, naturally-occurring leucinyl equivalents, and synthetic leucinyl equivalents.

R^2 is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, $-NHR^3$, and R^3.

The substituent R^3 is a pharmaceutically acceptable group. R^3 is independently selected with respect to size or length and secondary structure so that the present inventive polypeptide is able to bind to the IL-6 ligand with sufficient affinity to interfere competitively with IL-6 signaling under physiological conditions.

An amino acid residue equivalent thereof comprises a primary amine linked by one to three, preferably two, and more preferably one, methylenyl group(s) linked to a carboxylic acid, i.e., $NH_2-(CHR^a)_{1-3}-COO^-$, preferably $NH_2-(CHR^a)_2-COO^-$ and more preferably $NH_2-(CHR^a)-COO^-$. An amino residue (or its equivalent) is linked via a peptide bond (-C(O)NH-) to another amino acid residue (or its equivalent) or a polypeptide. An amino acid residue equivalent is an amino acid residue in which R^a is selected to have the same charge under physiological conditions as the amino acid residue, and, preferably, is selected to have a similar number of atoms as the side-chain substituent of the amino acid residue, i.e., plus or minus 50%, preferably plus or minus 20%. All amino acid residue equivalents preferably have only one R^a moiety that is not hydrogen (except for glycinyl equivalents for which R^a can be, and preferably is, repetitively selected as hydrogen, e.g., 3-amino proprionic acid; $NH2-(CH_2)_2-COO^-$). By way of example, an

argininyl equivalent residue is preferably selected from the group consisting of argininyl and lysinyl because (1) these residues are naturally-occurring and are encoded by a mammalian gene or genome, and (2) these residues have (a) similar sizes (arginine having 7 side-chain atoms (excluding hydrogen atoms) and lysine having 5, ((5-7)/(7) x 100% = 28%)), and (b) these residues are bases having similar pK values (about 12 and 10, respectively).

An argininyl residue or an argininyl equivalent residue can be either natural or synthetic. In addition to an argininyl residue *per se*, a natural amino acid residue equivalent to an argininyl residue includes, but is not limited to, histidinyl and lysinyl, and is preferably lysinyl. A synthetic amino acid residue equivalent to and argininyl residue includes, but is not limited to, d-forms of argininyl, lysinyl, and histidinyl residues, as well as L- and D-, but preferably L-, ornithinyl, citrullinyl, and homoargininyl residues. The skilled artisan will recognize additional argininyl equivalents from Figure 1.

A leucinyl residue or a leucinyl equivalent residue can be either natural or synthetic. Leucinyl equivalents include, but are not limited to, leucinyl, isoleucinyl, alaninyl, valinyl, norleucinyl, norvalinyl, sarcosinyl, β-alaninyl, and α-aminoisobutyryl. The skilled artisan will recognize additional leucinyl equivalents from Figure 1. Of course, in any given polypeptide, substitutions are preferably limited in number. For example, in the polypeptide R$^{\bullet}$R$^{\bullet}$L$^{\bullet}$L$^{\bullet}$L$^{\bullet}$R$^{\bullet}$, all of the R$^{\bullet}$ residues and all of the L$^{\bullet}$ residues are most preferably argininyl and leucinyl, respectively; less preferably,

one residue is other than argininyl or leucinyl, yet less preferably two or three residues are not argininyl or leucinyl, and least preferably four to six residues are not argininyl or leucinyl. Accordingly, a most preferred residue for R^* is an argininyl residue.

Similarly, L^* can be independently selected from the group consisting of leucinyl, isoleucinyl, and valinyl; preferably L^* is leucinyl or isoleucinyl; and most preferably, L^* is leucinyl. Additionally, L^* can optionally be a d-form amino acid residue, and/or a synthetic residue such as, e.g., an α-aminoisobutyryl residue.

The substituent R^3 can be any suitable pharmaceutically acceptable substituent. A pharmaceutically acceptably substituent need not, but can provide a function, such as homing to sites of inflammation, increasing the solubility in water of the present inventive polypeptide, and protecting side-chains of amino acid residues from oxidative or chemical attack. For example, a pharmaceutically acceptable substituent can be a biopolymer, such as a polypeptide, an RNA, a DNA, or a polysaccharide. Suitable polypeptides comprise fusion proteins, an antibody or fragment thereof, a cell adhesion molecule or a fragment thereof, or a peptide hormone. Suitable polysaccharides comprise polyglucose moieties, such as starch and derivatives thereof, such as heparin. R^3 also can be any suitable lipid or lipid-containing moiety, such as a lipid of a liposome or a vesicle, saccharide or disaccharide, or even a lipophilic moiety, such as a prostaglandin, a steroid hormone, or a derivative of either of the foregoing. Additionally, R^3

can be a nucleotide or a nucleoside, such as nicotine adenine dinucleotide or thymine. R^3 also can be a vitamin, such as vitamin C, thiamine, or nicotinic acid. A pharmaceutically acceptable substituent can be a synthetic organic moiety, such as t-butyl carbonyl, an acetyl moiety, quinine, or polystyrene and another biologically acceptable polymer. A pharmaceutically acceptable substituent also can be R^4, wherein R^4 is selected from the group consisting of a C_1-C_{18} alkyl, a C_2-C_{18} alkenyl, a C_2-C_{18} alkynyl, a C_6-C_{18} aryl, a C_7-C_{18} alkaryl, a C_7-C_{18} aralkyl, and a C_3-C_{18} cycloalkyl, wherein any of the foregoing R^3 groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur.

R^4 can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C_1-C_8 monoalkylamine moiety, a C_1-C_8 dialkylamine moiety, and a C_1-C_8 trialkylamine moiety.

A preferred polypeptide of the first embodiment $R^1R^*R^*L^*L^*L^*R^*R^2$ is RRLLLR, wherein R is argininyl and L is leucinyl. In a more preferred embodiment, R^2 of the formula $R^1R^*R^*L^*L^*L^*R^*R^2$ is a -(serinyl-valinyl-R^5), and R^5 is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 98 amino acid residues,

-NHR^4, and R^4, wherein R^4 is as defined above and can be substituted as described above.

In a second embodiment, the present invention provides a polypeptide of the formula $R^{10}R^{11}XVL^{*2}L^{*2}VR^{12}$, as well as pharmaceutically acceptable salts thereof. This embodiment is predicated, at least in part, on two surprising and unexpected discoveries. First, that a second domain of the α-chain of the IL-6 receptor that has the ability to bind to the IL-6 ligand comprises an important amino acid residue sequence -VLLV-, which naturally occurs in the context TKAVLLVRF. Second, that the binding affinity of this second domain is substantially increased if the lysinyl residue (in the larger subsequence) is replaced by an amino acid residue that does not have a side-chain that is basic under physiological conditions.

In this second embodiment, R^{10} and R^{12} are pharmaceutically acceptable substituents. Examples of pharmaceutically acceptable substituents are provided above with respect to R^3.

R^{11} is selected from the group consisting of synthetic and naturally-occurring amino acid residues that have an acidic or neutral side-chain under physiological conditions. For example, R^{11} can be selected from either the group consisting of alaninyl, asparaginyl, aspartyl, cysteinyl, glutaminyl, glutamyl, glycinyl, isoleucinyl, leucinyl, methioninyl, phenylalaninyl, prolinyl, serinyl, threoninyl, tryptophanyl, tyrosinyl, and valinyl, or the group consisting of norleucinyl, norvalinyl, sarcosinyl, β-alaninyl, α-aminoisobutyryl, γ aminopentane-1,5-dioyl,

homoserinyl, hydroxyprolinyl, α-carboxyglutamyl, O-phosphoserinyl, O-phosphothreoninyl, and O-phosphotyrosinyl.

Similarly, X can be any synthetic or naturally-occurring amino acid residue, such as any synthetic or naturally-occurring amino acid residue that has an acidic or neutral side-chain under physiological conditions. That is, X can be selected from the group consisting of suitable R^{11} residues, as well as from among the group consisting of argininyl, lysinyl, and histidinyl, or the group consisting of norleucinyl, norvalinyl, sarcosinyl, β-alaninyl, α-aminoisobutyryl, γ-aminopentane-1,5-dioyl, homoserinyl, hydroxyprolinyl, γ-carboxyglutamyl, O-phosphoserinyl, O-phosphothreoninyl, O-phosphotyrosinyl, ornithinyl, citrullinyl, and homoargininyl. However, X is preferably independently selected from the group denoted by R^{11}.

In the context of the formula $R^{10}R^{11}XVL^{*2}L^{*2}VR^{12}$, V is valinyl and L^{*2} is leucinyl or isoleucinyl, and preferably leucinyl. As noted above, each substituent of the polypeptide is selected such that this present inventive polypeptide inhibits the binding of IL-6 with IL-6 receptor under physiological conditions.

The pharmaceutically acceptable group R^{12} can optionally be the substituent R^{13}-R^{14}. Where R^{12} is R^{13}-R^{14}, R^{13} is selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is acidic or neutral under physiological conditions, including, but not limited to norleucinyl, sarcosinyl, β-alaninyl, α-aminoisobutyryl, γ-aminopentane-1,5-dioyl, homoserinyl, hydroxyprolinyl, α-

carboxyglutamyl, O-phosphoserinyl, O-phosphothreoninyl, and O-phosphotyrosinyl. Where R^{12} is R^{13}-R^{14}, R^{14} is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, -NHR^{15}, and R^{15}. R^{15} is a pharmaceutically acceptable substituent group (see R^3, *supra*). Preferably, R^{13} is selected from the group consisting of naturally-occurring amino acid residues having a side-chain that is acidic or neutral under physiological conditions. Alternatively, R^{13} is preferably selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain consisting of a C_1-C_6 straight-chained or branched alkyl moiety; for example, from the group consisting of glycinyl, alaninyl, isoleucinyl, leucinyl, valinyl, norleucinyl, sarcosinyl, β-alaninyl, and α-aminoisobutyryl. The polypeptide in which R^{13} is alaninyl is among the preferred polypeptides of the second embodiment.

In one polypeptide of the second embodiment, R^{15} is R^{16}, and R^{16} is selected from the group consisting of hydrogen, a C_1-C_{18} alkyl, a C_2-C_{18} alkenyl, a C_2-C_{18} alkynyl, a C_6-C_{18} aryl, a C_7-C_{18} alkaryl, a C_7-C_{18} aralkyl, and a C_3-C_{18} cycloalkyl, wherein any of the foregoing R^{16} groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur.

Optionally, R^{16} can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate

moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C_1-C_8 monoalkylamine moiety, a C_1-C_8 dialkylamine moiety, and a C_1-C_8 trialkylamine moiety.

In another polypeptide of the second embodiment, R^{10} is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, $R^{17}C(O)$-, and R^{17}, wherein R^{17} is a pharmaceutically acceptable substituent group (see R^3, *supra*).

Similarly to R^{16}, R^{17} can be selected from the group consisting of hydrogen, a C_1-C_{18} alkyl, a C_2-C_{18} alkenyl, a C_2-C_{18} alkynyl, a C_6-C_{18} aryl, a C_7-C_{18} alkaryl, a C_7-C_{18} aralkyl, and a C_3-C_{18} cycloalkyl, wherein any of the foregoing R^{17} groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur. In a preferred embodiment, R^{17} is hydrogen.

Optionally, R^{17} can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C_1-C_8 monoalkylamine moiety, a C_1-C_8 dialkylamine moiety, and a C_1-C_8 trialkylamine moiety.

In a third embodiment, the present invention provides a polypeptide of the formula $R^{20}R^{21}L^*R^*Y^*R^*A^*E^*R^*S^*R^{22}$. This embodiment is predicated, at

least in part, on three surprising and unexpected discoveries. First, that a third domain within the IL-6 receptor has the ability to bind to the IL-6 ligand and this domain has the essential core amino acid residue sequence -LRAERS-, which naturally occurs in the larger subsequence -FELRAERSKT. Second, that the affinity of this domain for the IL-6 ligand can be substantially enhanced if the acidic side chain of the first glutamyl residue in the larger sequence is eliminated or preferably is replaced by a small hydrophobic side-chain (e.g., as possessed by alanine). Third, that the lysinyl residue is preferably present and more preferably has a side-chain that is basic under physiological conditions.

In this third embodiment, R^{20} and R^{22} are pharmaceutically acceptable substituents. The substituent R^{21} is selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is neutral or basic under physiological conditions, which includes, but clearly is not limited to, norleucinyl, norvalinyl, sarcosinyl, β-alaninyl, α-aminoisobutyryl, homoserinyl, hydroxyprolinyl, ornithinyl, citrullinyl, and homoargininyl. Preferably, R^{21} is alaninyl.

Additionally, L^*, Y^*, E^*, and S^* are each independently selected from the group consisting of synthetic and naturally-occurring amino acid residues. L^* is preferably leucinyl or isoleucinyl. More preferably, L^* is leucinyl. The substituent Y^* is preferably selected from the group consisting of tyrosinyl, phenylalaninyl, tryptophanyl, and α-aminoisobutyryl. More preferably, Y^* is tyrosinyl or phenylalaninyl, and most preferably,

tyrosinyl. The substituent E* is preferably selected from the group consisting of synthetic and naturally-occurring amino acid residues having acidic side-chains under physiological conditions. For example, E* can be selected from the group consisting of glutamyl, aspartyl, γ aminopentane-1,5-dioyl, O-phosphoserinyl, O-phosphothreoninyl, and O-phosphotyrosinyl. More preferably, E* is selected from the group consisting of glutamyl, aspartyl, and γ aminopentane-1,5-dioyl. Yet more preferably, E* is glutamyl. The substituent S* is selected from the group consisting of serinyl, threoninyl, phosphoserinyl, and phosphothreoninyl, and preferably is serinyl. The substituent A* is selected from the group consisting of alaninyl, glycinyl, and valinyl, and preferably is alaninyl.

Preferably, R^{20} is selected from the group consisting of a polypeptide of from 1 to about 100 amino acid residues, hydrogen, $R^{23}C(O)$-, and R^{23}. Similarly, R^{22} is preferably selected from the group consisting of a polypeptide of from 1 to about 100 amino acid residues, hydrogen, $-NHR^{23}$, and R^{23}.

The substituent R^{23} can be selected from the group consisting of a C_1-C_{18} alkyl, a C_2-C_{18} alkenyl, a C_2-C_{18} alkynyl, a C_6-C_{18} aryl, a C_7-C_{18} alkaryl, a C_7-C_{18} aralkyl, and a C_3-C_{18} cycloalkyl, wherein any of the foregoing R^{23} groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur.

R^{23} can be substituted by one to about six substituents, which can be the same or different,

selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C_1-C_8 monoalkylamine moiety, a C_1-C_8 dialkylamine moiety, and a C_1-C_8 trialkylamine moiety.

R* is independently selected from the group consisting of synthetic or naturally-occurring amino acid residues having a side-chain that is basic under physiological conditions; for example, argininyl, lysinyl, ornithinyl, citrullinyl, or homoargininyl. Preferably, R* is selected from the group consisting of argininyl and lysinyl. More preferably, R* is argininyl.

A* is selected from the group consisting of alaninyl, glycinyl, isoleucinyl, leucinyl, valinyl, norleucinyl, norvalinyl, sarcosinyl, β-alaninyl, and α-aminoisobutyryl. Preferably, A* is alaninyl.

Additionally, the polypeptide of the third embodiment of the present invention can comprise additional polypeptides or protein motifs. Preferably, the present inventive polypeptide does not comprise more than about 200, and preferably more than about 50, additional amino acid residues that have an amino acid residue sequence that is identical (or at least 60% identical over a span of five or ten amino acid residues) to another amino acid residue sequence from the same chain of the IL-6 receptor.

In a fourth embodiment, the present invention provides a polypeptide, which comprises a sequence that inhibits binding of IL-6 ligand with IL-6 receptor under

physiological conditions. The sequence comprises at least a polypeptide of the formula I*A*I*V*L*R*F*. This embodiment is predicated, at least in part, on the surprising and unexpected discovery that a fourth domain of the IL-6 receptor occurs in the membrane-associated region of the receptor, and this domain is centered about a region of the receptor having an amino acid residue sequence of IAIVLRFK. This embodiment is further predicated on the surprising and unexpected discovery that this domain is highly tolerant of amino acid residue substitutions. For example, the basic residues of this sequence (i.e., argininyl and lysinyl) can be replaced by a non-conservative alaninyl substitution, which has the surprising effect of increasing the affinity of the domain for the IL-6 ligand.

In this fourth embodiment I*, L*, and V* are independently selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain consisting of a C_1-C_6 straight-chain or branched alkyl moiety.

R* is independently selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is basic under physiological conditions. For example, R* can be selected from the group consisting of argininyl, lysinyl, ornithinyl, citrullinyl, and homoargininyl. When R* is to be translated from a nucleic acid, R* preferably is selected from the group consisting of argininyl and lysinyl. R* is more preferably argininyl.

A* is selected from the group consisting of alaninyl, glycinyl, isoleucinyl, leucinyl, valinyl, norleucinyl,

norvalinyl, sarcosinyl, β-alaninyl, and α-aminoisobutyryl.

F* is selected from the group consisting of tyrosinyl, phenylalaninyl, tryptophanyl, and α-aminoisobutyryl.

Preferably, at least four of the seven substituents, more preferably at least five substituents, yet more preferably at least six substituents of I*A*I*V*L*R*F*, are selected such that I* is isoleucinyl, A* is alaninyl, V* is valinyl, L* is leucinyl, R* is argininyl, and F* phenylalaninyl. Of course, all seven amino acid residues can be selected such that I*A*I*V*L*R*F* is IAIVLRFK. The polypeptide is preferably selected such that it is small enough to bind effectively to IL-6 and does not comprise unnecessary extra atoms (making synthesis and processing of the polypeptide easier). The polypeptide preferably comprises less than about 200 amino acid residues, alternatively less than about 100 amino acid residues, alternatively less than about 30 amino acid residues, and alternatively less than about 16 amino acid residues that have a sequence that is identical to that of a region of the α-chain of the IL-6 receptor.

Surprisingly, the affinity of the polypeptide for binding with IL-6 increases if any one, preferably two, and more preferably three, amino acid residues are bound via peptide bonds to the carboxyl-terminus of the sequence I*A*I*V*L*R*F*. Accordingly, the polypeptide preferably comprises at least the sequence IAIVLRFKXX in which X is any synthetic or naturally-occurring amino acid residue, as defined above, and preferably a synthetic or naturally-occurring amino acid residue of

the formula NH_2-(CHR^a)-COO^-. Optionally, the sequence can comprise an amino-terminal tripeptide of the formula LLC-, or conservatively or neutrally substituted equivalents of LLC-. In this regard, the sequence can comprise at least the sequence LLCIAIVLRFK. Additionally, the sequence can comprise at least the sequence FGTLLCIAIVLRFKKT.

A fifth embodiment of the present invention is predicated on the surprising and unexpected discovery that the amino acid sequence SVIILKYNIQY, which is a subsequence of the β-chain amino acid sequence of the IL-6 receptor, is critical in the binding between IL-6 ligand and IL-6 receptor. Accordingly, the present invention also provides a polypeptide that inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions. The present inventive polypeptide of this fifth embodiment comprises the sequence SVIILKYNIQY and has an amino acid residue sequence of up to about 200 amino acid residues, preferably about 100 residues, more preferably about 50 residues, and optionally no or essentially no additional residues, that are identical to the β-chain of the IL-6 receptor or alternatively are at least about 60% identical over a span of about five or ten contiguous amino acid residues.

Biochemical analysis of this sequence revealed that the binding interaction is somewhat stronger if the sequence SVIILKYNIQY is extended on the amino terminus to include the sequence PSIK-. Accordingly, the present invention also provides a polypeptide of this fifth embodiment comprising the sequence PSIKSVIILKYNIQY.

Similar analyses further defined a region governing the binding between IL-6 ligand and its receptor. These analyses resulted in the identification and provision of polypeptides comprising the sequences WTNPSIKSVIILKYNIQY and KLTWTNPSIKSVIILKYNIQY, and up to about 200 amino acid residues that have an identical residue sequence to the sequence of the β-chain of the IL-6 receptor. Preferably, the polypeptides comprising the recited sequences comprise up to about 100 amino acid residues, more preferably, up to about 50 amino acid residues, from the IL-6 receptor β-chain sequence. Optionally, the polypeptide comprises no other, or essentially no other, sequence of amino acid residues that has an identical sequence to the sequence of the IL-6 receptor β-chain over a continuous stretch of five, or more preferably three, amino acid residues other than the sequences explicitly recited above. Additionally, the present inventive sequences preferably do not comprise a region of higher than about 60% homology to the IL-6 receptor over a stretch of at least five or ten contiguous amino acid residues, outside the region of the IL-6 receptor β-chain sequences explicitly recited above.

Alternatively, the present inventive β-chain polypeptides comprise a sequence consisting essentially of the recited sequence and polypeptides from other sources or origins that primarily contribute a function that is not directly related to IL-6 function or signaling.

In additional (sixth, seventh, and eighth) embodiments, the present invention provides a polypeptide of up to about 200 amino acid residues having a sequence

that is identical to a portion of the sequence TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL, QLPVDVQNGFIRNYTIFYRTIIGN, or IVVPVCLAFLLTTLLGVLFCFNKRDLIKKHIWPNVPDPSKSHIA, and that inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions. The portion of the sequence can be any suitable size. For example, the portion of the amino acid sequence can be about a 6-mer, about a 12-mer, about an 18-mer, or about a 24-mer. An "n"-mer, as is understood in the art, is an oligopolymer consisting of "n" monomeric components or residues. Thus, a polypeptide comprising a portion of any of the preceding sequences that is a 6-mer, would comprise an amino acid sequence of any six adjacent residues of any one of the three preceding amino acid sequences. Preferably, the polypeptide comprises no more than about 100 amino acid residues, and more preferably no more than about 50 amino acid residues, having a sequence identical to that of the IL-6 receptor β-chain.

Conservative or neutral amino acid substitutions that do not destroy the ability of any of the above-described polypeptides to bind to IL-6 can be made. The replacement residues that substitute for the amino acid residues explicitly recited above can be either synthetic or naturally-occurring. Preferably, the number of substitutions is kept to a minimum, e.g., from 1 to about 6 conservative or neutral substitutions, and more preferably from 1 to about 3 conservative or neutral amino acid residue substitutions. While the residues substituted for the recited amino acid residues can be natural or synthetic, natural residues are preferred in

those instances in which it is desirable for the amino acid residues to be encoded by a nucleic acid.

Additionally, any embodiment of the foregoing present inventive polypeptide can further comprise a pharmaceutically acceptable substituent, which is selected so that the polypeptide retains the ability to inhibit the binding of IL-6 ligand with IL-6 receptor under physiological conditions.

Also provided by the present invention is a nucleic acid that encodes an above-described polypeptide, which consists of naturally-occurring amino acid residues. The nucleic acid can be expressed in a cell.

In another embodiment, the present invention also provides a vector comprising a nucleic acid molecule as described above. A nucleic acid molecule as described above can be cloned into any suitable vector and can be used to transduce, transform, or transfect any suitable host. The selection of vectors and methods to construct them are commonly known to persons of ordinary skill in the art and are described in general technical references (see, in general, "Recombinant DNA Part D," *Methods in Enzymology*, Vol. 153, Wu and Grossman, eds., Academic Press (1987)). Desirably, the vector comprises regulatory sequences, such as transcription and translation initiation and termination codons, which are specific to the type of host (e.g., bacterium, fungus, plant, or animal) into which the vector is to be inserted, as appropriate and taking into consideration whether the vector is DNA or RNA. Preferably, the vector comprises regulatory sequences that are specific to the genus of the host. Most preferably, the vector comprises

regulatory sequences that are specific to the species of the host and is optionally optimized for the expression of an above-described polypeptide.

Constructs of vectors, which are circular or linear, can be prepared to contain an entire nucleic acid sequence as described above or a portion thereof ligated to a replication system that is functional in a prokaryotic or eukaryotic host cell. Replication systems can be derived from ColE1, 2 mμ plasmid, λ, SV40, bovine papilloma virus, and the like.

Suitable vectors include those designed for propagation and expansion, or for expression, or both. A preferred cloning vector is selected from the group consisting of the pUC series, the pBluescript series (Stratagene, LaJolla, CA), the pET series (Novagen, Madison, WI), the pGEX series (Pharmacia Biotech, Uppsala, Sweden), and the pEX series (Clonetech, Palo Alto, CA). Examples of animal expression vectors include pEUK-C1, pMAM and pMAMneo (Clonetech, Palo Alto, CA).

An expression vector can comprise a native or nonnative promoter operably linked to a nucleic acid molecule encoding an above-described polypeptide. The selection of promoters, e.g., strong, weak, inducible, tissue-specific and developmental-specific, is within the skill in the art. Similarly, the combining of a nucleic acid molecule as described above with a promoter is also within the skill in the art.

The nucleic acid encoding the polypeptide can be operably linked to a signal sequence that causes secretion of at least the polypeptide by a cell in which the nucleic acid is expressed. Signal sequences

(alternatively called secretion sequences) are well-known in the art.

Alternatively, the nucleic acid comprises or encodes an antisense nucleic acid molecule or a ribozyme that is specific for a naturally-occurring, specified amino acid sequence of an above-described polypeptide. A nucleic acid sequence introduced in antisense suppression generally is substantially identical to at least a portion of the endogenous gene or gene to be repressed, but need not be identical. Thus, the vectors can be designed such that the inhibitory effect applies to other proteins within a family of genes exhibiting homology or substantial homology to the target gene. The introduced sequence also need not be full-length relative to either the primary transcription product or fully processed mRNA. Generally, higher homology can be used to compensate for the use of a shorter sequence. Furthermore, the introduced sequence need not have the same intron or exon pattern, and homology of non-coding segments will be equally effective.

Ribozymes also have been reported to have use as a means to inhibit expression of endogenous genes. It is possible to design ribozymes that specifically pair with virtually any target RNA and cleave the phosphodiester backbone at a specific location, thereby functionally inactivating the target RNA. In carrying out this cleavage, the ribozyme is not itself altered and is, thus, capable of recycling and cleaving other molecules, making it a true enzyme. The inclusion of ribozyme sequences within antisense RNAs confers RNA-cleaving activity upon them, thereby increasing the activity of

the constructs. The design and use of target RNA-specific ribozymes is described in Haseloff et al., *Nature* 334: 585-591 (1988).

Further provided by the present invention is a composition comprising an above-described polypeptide or nucleic acid and a carrier therefor. Another composition provided by the present invention is a composition comprising an antibody to an above-described polypeptide, an anti-antibody to an above described polypeptide, or a solid support matrix to which is attached an above-described polypeptide or an anti-antibody to the polypeptide sequence RRLLLR, RXVLLV, LRYRAERS, IAIVLRF, SVIILKYNIQY, PSIKSVIILKYNIQY, WTNPSIKSVIILKYNIQY, KLTWTNPSIKSVIILKYNIQY, TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL, QLPVDVQNGFIRNYTIFYRTIIGN, or IVVPVCLAFLLTTLLGVLFCFNKRDLIKKHIWPNVPDPSKSHIA.

Antibodies can be generated in accordance with methods known in the art. See, for example, Benjamin, *In Immunology: a short course*, Wiley-Liss, NY, 1996, pp. 436-437; Kuby, *In Immunology*, 3rd. ed., Freeman, NY, 1997, pp. 455-456; Greenspan et al., *FASEB J.* 7: 437-443 (1993); and Poskitt, *Vaccine* 9: 792-796 (1991). Anti-antibodies (i.e., anti-idiotypic antibodies) also can be generated in accordance with methods known in the art (see, for example, Benjamin, *In Immunology: a short course*, Wiley-Liss, NY, 1996, pp. 436-437; Kuby, *In Immunology*, 3rd. ed., Freeman, NY, 1997, pp. 455-456; Greenspan et al., FASEB J., 7, 437-443, 1993; Poskitt, Vaccine, 9, 792-796, 1991; and Madiyalakan et al., *Hybridonor* 14: 199-203 (1995) ("Anti-idiotype induction

therapy")). Such antibodies can be obtained and employed either in solution-phase or coupled to a desired solid-phase matrix. Having in hand such antibodies, one skilled in the art will further appreciate that such antibodies, using well-established procedures (e.g., such as described by Harlow and Lane (1988, supra), are useful in the detection, quantification, or purification of IL-6 ligand, IL-6 receptor, conjugates of each and host cells transformed to produce IL-6 receptor or a derivative thereof. Such antibodies are also useful in a method of prevention or treatment of a disease or dysfunction in an animal in which it is desirable to inhibit IL-6 signaling or function, as provided herein.

In view of the above, the present invention also provides a method of producing an antibody to the specific amino acid sequence of an above-described polypeptide. The method comprises administering an above-described polypeptide to an animal. The animal generates anti-polypeptide antibodies. Such an antibody can be administered to an animal to prevent or treat a disease or dysfunction in an animal in which it is desirable to inhibit IL-6 signaling or function, as provided herein.

Although nonhuman antibodies are useful for prophylactic or therapeutic treatment in humans, their favorable properties, in certain instances, can be further enhanced and/or their adverse properties further diminished, through "humanization" strategies, such as those recently reviewed by Vaughan, Nature Biotech., 16, 535-539, 1998.

Prior to administration to an animal, such as a mammal, in particular a human, an above-described polypeptide, nucleic acid or antibody can be formulated into various compositions by combination with appropriate carriers, in particular, pharmaceutically acceptable carriers or diluents, and can be formulated to be appropriate for either human or veterinary applications.

Thus, a composition for use in the method of the present invention can comprise one or more of the aforementioned polypeptides, nucleic acids or antibodies, preferably in combination with a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well-known to those skilled in the art, as are suitable methods of administration. The choice of carrier will be determined, in part, by whether a polypeptide or a nucleic acid is to be administered, as well as by the particular method used to administer the composition. One skilled in the art will also appreciate that various routes of administering a composition are available, and, although more than one route can be used for administration, a particular route can provide a more immediate and more effective reaction than another route. Accordingly, there are a wide variety of suitable formulations of compositions that can be used in the present inventive methods.

A composition in accordance with the present invention, alone or in further combination with one or more other active agents, can be made into a formulation suitable for parenteral administration, preferably intraperitoneal administration. Such a formulation can include aqueous and nonaqueous, isotonic sterile

injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and nonaqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives.

The formulations can be presented in unit dose or multi-dose sealed containers, such as ampules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, water, for injections, immediately prior to use. Extemporaneously injectable solutions and suspensions can be prepared from sterile powders, granules, and tablets, as described herein.

A formulation suitable for oral administration can consist of liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, saline, or fruit juice; capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as solid or granules; solutions or suspensions in an aqueous liquid; and oil-in-water emulsions or water-in-oil emulsions. Tablet forms can include one or more of lactose, mannitol, corn starch, potato starch, microcrystalline cellulose, acacia, gelatin, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible carriers.

Similarly, a formulation suitable for oral administration can include lozenge forms, which can

comprise the active ingredient in a flavor, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier; as well as creams, emulsions, gels, and the like containing, in addition to the active ingredient, such carriers as are known in the art.

An aerosol formulation suitable for administration via inhalation also can be made. The aerosol formulation can be placed into a pressurized acceptable propellant, such as dichlorodifluoromethane, propane, nitrogen, and the like.

A formulation suitable for topical application can be in the form of creams, ointments, or lotions.

A formulation for rectal administration can be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate. A formulation suitable for vaginal administration can be presented as a pessary, tampon, cream, gel, paste, foam, or spray formula containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

Important general considerations for design of delivery systems and compositions, and for routes of administration, for polypeptide drugs also apply (Eppstein, CRC Crit. Rev. Therapeutic Drug Carrier Systems 5, 99-139, 1988; Siddiqui et al., CRC Crit. Rev. Therapeutic Drug Carrier Systems 3, 195-208, 1987); Banga et al., Int. J. Pharmaceutics 48, 15-50, 1988; Sanders, Eur. J. Drug Metab. Pharmacokinetics 15, 95-102, 1990;

Verhoef, Eur. J. Drug Metab. Pharmacokinetics 15, 83-93, 1990). The appropriate delivery system for a given polypeptide will depend upon its particular nature, the particular clinical application, and the site of drug action. As with any protein drug, oral delivery will likely present special problems, due primarily to instability in the gastrointestinal tract and poor absorption and bioavailability of intact, bioactive drug therefrom. Therefore, especially in the case of oral delivery, but also possibly in conjunction with other routes of delivery, it will be necessary to use an absorption-enhancing agent in combination with a given polypeptide. A wide variety of absorption-enhancing agents have been investigated and/or applied in combination with protein drugs for oral delivery and for delivery by other routes (Verhoef (1990), *supra*; van Hoogdalem, *Pharmac. Ther.* 44: 407-443, (1989); Davis, *J. Pharm. Pharmacol.* 44(Suppl. 1): 186-190, (1992). Most commonly, typical enhancers fall into the general categories of (a) chelators, such as EDTA, salicylates, and N-acyl derivatives of collagen, (b) surfactants, such as lauryl sulfate and polyoxyethylene-9-lauryl ether, (c) bile salts, such as glycholate and taurocholate, and derivatives, such as taurodihydrofusidate, (d) fatty acids, such as oleic acid and capric acid, and their derivatives, such as acylcarnitines, monoglycerides, and diglycerides, (e) non-surfactants, such as unsaturated cyclic ureas, (f) saponins, (g) cyclodextrins, and (h) phospholipids.

Other approaches to enhancing oral delivery of protein drugs can include the aforementioned chemical

modifications to enhance stability to gastrointestinal enzymes and/or increased lipophilicity. Alternatively, the protein drug can be administered in combination with other drugs or substances that directly inhibit proteases and/or other potential sources of enzymatic degradation of proteins. Yet another alternative approach to prevent or delay gastrointestinal absorption of protein drugs is to incorporate them into a delivery system that is designed to protect the protein from contact with the proteolytic enzymes in the intestinal lumen and to release the intact protein only upon reaching an area favorable for its absorption. A more specific example of this strategy is the use of biodegradable microcapsules or microspheres, both to protect vulnerable drugs from degradation, as well as to effect a prolonged release of active drug (Deasy, in Microencapsulation and Related Processes, Swarbrick, ed., Marcell Dekker, Inc.: New York, 1984, pp. 1-60, 88-89, 208-211). Microcapsules also can provide a useful way to effect a prolonged delivery of a protein drug, such as an above-described polypeptide, after injection (Maulding, J. Controlled Release 6, 167-176, 1987).

In view of the above, the present invention further provides a method of prophylactically or therapeutically inhibiting IL-6 signaling in a mammal in need thereof. The method comprises administering to the mammal an IL-6 signaling-inhibiting effective amount of an above-described polypeptide, nucleic acid, or antibody to an above-described polypeptide or a nucleic acid encoding such a polypeptide.

The dose administered to an animal, such as a mammal, particularly a human, in the context of the present invention should be sufficient to effect a therapeutic or prophylactic (which desirably, but not necessarily, means absolute prevention as any degree of inhibition of IL-6 signaling in a mammal in need thereof is deemed beneficial) response in the individual over a reasonable time frame. The dose will be determined by the particular polypeptide, nucleic acid or antibody, administered, the severity of any existing disease state, as well as the body weight and age of the individual. The size of the dose also will be determined by the existence of any adverse side effects that may accompany the use of the particular polypeptide, nucleic acid or antibody employed. It is always desirable, whenever possible, to keep adverse side effects to a minimum.

The dosage can be in unit dosage form, such as a tablet or capsule. The term "unit dosage form" as used herein refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of a vector, alone or in combination with other active agents, calculated in an amount sufficient to produce the desired effect in association with a pharmaceutically acceptable diluent, carrier, or vehicle. The specifications for the unit dosage forms of the present invention depend on the particular embodiment employed and the effect to be achieved, as well as the pharmacodynamics associated with each polypeptide, nucleic acid or antibody in the host. The dose administered should be an "IL-6 signaling-inhibiting effective amount" of an above-described active

agent to achieve an "effective level" in the individual patient.

With respect to the above methods, sufficient amounts can be determined in accordance with methods known in the art. Similarly, the sufficiency of an immune response in an animal also can be assessed in accordance with methods known in the art. Either one of the above methods can further comprise concurrent, pre- or post-treatment with an adjuvant to enhance the immune response (see, for example, Harlow et al. (1988), *supra*).

Since the "effective level" is used as the preferred endpoint for dosing, the actual dose and schedule can vary, depending on interindividual differences in pharmacokinetics, drug distribution, and metabolism. The "effective level" can be defined, for example, as the blood or tissue level desired in the patient that corresponds to a concentration of one or more polypeptides, nucleic acids or antibodies according to the invention. The "effective level" for a polypeptide, nucleic acid or antibody of the present invention also can vary when the compositions of the present invention are used in combination with other known active agents.

One skilled in the art can easily determine the appropriate dose, schedule, and method of administration for the exact formulation of the composition being used, in order to achieve the desired "effective level" in the individual patient. One skilled in the art also can readily determine and use an appropriate indicator of the "effective level" of a polypeptide, nucleic acid or antibody of the present invention by a direct or indirect

analysis of appropriate patient samples (e.g., blood and/or tissues).

It also will be appreciated by one skilled in the art that an above-described nucleic acid can be inserted *ex vivo* into animal cells, such as mammalian cells, in particular human cells, previously removed from such an animal. Such transformed autologous or homologous host cells, reintroduced into the animal or human, will express directly the corresponding polypeptide *in vivo*. The feasibility of such a therapeutic strategy to deliver a therapeutic amount of an agent in close proximity to the desired target cells has been demonstrated in studies with cells engineered *ex vivo* to express sCD4 (Morgan et al., (1994), *supra*). As an alternative to *ex vivo* insertion of the DNA sequences of the present invention, such sequences can be inserted into cells directly *in vivo*, such as by use of an appropriate viral or other suitable vector. Such cells transfected *in vivo* are expected to produce effective amounts of an above-described polypeptide directly *in vivo*.

Given the present disclosure, it will be additionally appreciated that an above-described nucleic acid sequence can be inserted into suitable nonmammalian host cells, and that such host cells will express therapeutic or prophylactic amounts of the desired polypeptide directly *in vivo* within a desired body compartment of an animal, in particular a human.

In addition, the present invention provides a method of removing IL-6 ligand from a bodily fluid of a mammal. The method comprises extracorporeally contacting the bodily fluid of the animal with a solid-support matrix to

which is attached an above-described polypeptide or an anti-antibody to the polypeptide sequence RRLLLR, RXVLLV, LRYRAERS, IAIVLRF, SVIILKYNIQY, PSIKSVIILKYNIQY, WTNPSIKSVIILKYNIQY, KLTWTNPSIKSVIILKYNIQY, TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL, QLPVDVQNGFIRNYTIFYRTIIGN, or IVVPVCLAFLLTTLLGVLFCFNKRDLIKKHIWPNVPDPSKSHIA. Alternatively, the bodily fluid can be contacted with the polypeptide or anti-antibody in solution and then the solution can be contacted with a solid support matrix to which is attached a means to remove the polypeptide or anti-antibody to which is bound IL-6 ligand from the bodily fluid. The method further comprises separating the bodily fluid and the solid support matrix by any suitable means.

Methods of attaching an above-described polypeptide or an anti-antibody to a solid support matrix are known in the art. "Attached" is used herein to refer to attachment to (or coupling to) and immobilization in or on a solid support matrix. See, for example, Harris, in Poly(Ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications, Harris, ed., Plenum Press: New York (1992), pp. 1-14) and international patent application WO 91/02714 (Saxinger). Diverse applications and uses of functional polypeptides attached to or immobilized on a solid support matrix are exemplified more specifically for poly(ethylene glycol) conjugated proteins or peptides in a review by Holmberg et al. (In Poly(Ethylene Glycol) Chemistry: Biotechnical and Biomedical Applications, Harris, ed., Plenum Press: New York, 1992, pp. 303-324).

EXAMPLES

The following examples further illustrates the present invention but, of course, should not be construed as limiting the scope of the claimed invention in any way.

Synthetic peptide arrays were constructed in 96-well microtiter plates in accordance with the method set forth in WO 91/02714 (Saxinger), and used to test the binding of recombinant human IL-6 that had been labeled with radioactive iodine (radiolabeling by standard methods). After incubating the radiolabeled IL-6 ligand in a well with each synthetic peptide, a washing step was performed to remove unbound label, and the relative level of radioactivity remaining in each well of the plate was evaluated to determine the relative affinity of each peptide for IL-6 ligand. The synthesis of the peptides and the quantity of binding between the synthetic peptides and IL-6 ligand were found to be suitably reproducible, precise, and sensitive. Initial screening of the entire primary sequence of the IL-6 receptor molecule, taken 21 amino acid residues at a time, identified active binding sequences in four regions of the receptor corresponding to amino acid residues 66-86 (AAGSHPSRWAGMGRRLLLRSV), 136-156 (PRSTPSLTTKAVLLVRKFQNS), 246-266 (SSFYRLRFELRYRAERSKTFT), and 371-391 (GGSLAFGTLLCIAIVLRFKKT) (hereinafter domains I, II, III, and IV).

The authenticity of the binding signal was confirmed, at least for domains I-III, by demonstrating that antibodies that specifically bind to IL-6 ligand

were able to inhibit the binding reactions. The binding between domain IV and IL-6 ligand was not similarly shown to be authentic because domain IV resides in the transmembrane region of the protein and is not believed to have been present in the soluble receptor used as an immunogen to raise the antibodies to IL-6 ligand.

Each of the four binding domains was analyzed in detail, which is set forth in these examples. First, serial truncations (or nested truncations) were performed from each end of the peptides to determine the location of the critical binding residues within each domain. Second, each amino acid residue in the critical regions of each domain were serially replaced by an alaninyl residue to indicate whether the side-chain of the residue at each particular location is likely to be essential or important to the mechanism of binding.

Example 1

This example provides data identifying domain I, as well as amino acid residues that are essential and/or important in the binding of domain I to human IL-6.

Peptide Identifier	Peptide Sequence	Counts/minute bound
A1:	AAGSHPSRWAGMGRRLLLRSV	10739
A2:	AAGSHPSRWAGMGRRLLLRS	9764
A3:	AAGSHPSRWAGMGRRLLLR	8007
A4:	AAGSHPSRWAGMGRRLLL	5276
A5:	AAGSHPSRWAGMGRRLL	2747
A6:	AAGSHPSRWAGMGRRL	1753
A7:	AAGSHPSRWAGMGRR	1344
A8:	AAGSHPSRWAGMGR	1478
A9:	AAGSHPSRWAGMG	1474
A10:	AAGSHPSRWAGM	1444
A11:	AAGSHPSRWAG	1427
A12:	AAGSHPSRWA	1328

A13:	AAGSHPSRW	1520
A14:	AAGSHPSR	1353
A15:	AAGSHPS	1316
A16:	AAGSHP	1574
A17:	AAGSHPSRWAGMGRRLLLRSV	10884
A18:	AGSHPSRWAGMGRRLLLRSV	13393
A19:	GSHPSRWAGMGRRLLLRSV	10994
A20:	SHPSRWAGMGRRLLLRSV	12048
A21:	HPSRWAGMGRRLLLRSV	11969
A22:	PSRWAGMGRRLLLRSV	11087
A23:	SRWAGMGRRLLLRSV	8272
A24:	RWAGMGRRLLLRSV	12069
A25:	WAGMGRRLLLRSV	12166
A26:	AGMGRRLLLRSV	7623
A27:	GMGRRLLLRSV	6820
A28:	MGRRLLLRSV	7136
A29:	GRRLLLRSV	5367
A30:	RRLLLRSV	5972
A31:	RLLLRSV	5464
A32:	LLLRSV	1599
A33:	AAGSHPSRWAGMGRRLLLRSV	10213
A34:	AAGSHPSRWAGMGRRLLLRS<u>A</u>	11797
A35:	AAGSHPSRWAGMGRRLLLR<u>A</u>V	11201
A36:	AAGSHPSRWAGMGRRLLL<u>A</u>SV	4895
A37:	AAGSHPSRWAGMGRRLL<u>A</u>RSV	7728
A38:	AAGSHPSRWAGMGRRL<u>A</u>LRSV	7079
A39:	AAGSHPSRWAGMGRR<u>A</u>LLRSV	5283
A40:	AAGSHPSRWAGMGR<u>A</u>LLLRSV	4247
A41:	AAGSHPSRWA<u>GMGA</u>RLLLRSV	4461
A42:	AAGSHPSRWAGM<u>ARRLLLRSV</u>	12259
A43:	AAGSHPSRWAG<u>A</u>GRRLLLRSV	13521
A44:	AAGSHPSRWA<u>A</u>MGRRLLLRSV	11854
A45:	AAGSHPSR<u>A</u>AGMGRRLLLRSV	8040
A46:	AAGSHPS<u>A</u>WAGMGRRLLLRSV	9523
A47:	AAGSHP<u>A</u>RWAGMGRRLLLRSV	11291

These data indicate that the sequence RRLLLR is a critical binding region within domain I, that domain I is preferably flanked on the amino-terminus by a pharmaceutically acceptable substituent equivalent in size to three amino acid residues, e.g., any three amino acid residues, and is preferably flanked on the carboxyl-

terminus by a pharmaceutically acceptable substituent equivalent in size to at least one amino acid residue, and preferably two or three or more amino acid residues.

Example 2

This example provides data identifying the critical binding regions of domain II, as well as which residues within the critical binding domain that are essential and/or important in the binding of human IL-6 to IL-6 receptor within domain II.

Peptide Identifier	Peptide Sequence	Counts/minute bound
B1:	PRSTPSLTTKAVLLVRKFQNS	10790
B2:	PRSTPSLTTKAVLLVRKFQN	7930
B3:	PRSTPSLTTKAVLLVRKFQ	7075
B4:	PRSTPSLTTKAVLLVRKF	4689
B5:	PRSTPSLTTKAVLLVRK	3962
B6:	PRSTPSLTTKAVLLVR	4355
B7:	PRSTPSLTTKAVLLV	3401
B8:	PRSTPSLTTKAVLL	1846
B9:	PRSTPSLTTKAVL	1402
B10:	PRSTPSLTTKAV	1216
B11:	PRSTPSLTTKA	1240
B12:	PRSTPSLTTK	1313
B13:	PRSTPSLTT	1053
B14:	PRSTPSLT	930
B15:	PRSTPSL	985
B16:	PRSTPS	1015
B17:	PRSTPSLTTKAVLLVRKFQNS	12347
B18:	RSTPSLTTKAVLLVRKFQNS	12958
B19:	STPSLTTKAVLLVRKFQNS	12150
B20:	TPSLTTKAVLLVRKFQNS	12885
B21:	PSLTTKAVLLVRKFQNS	13294
B22:	SLTTKAVLLVRKFQNS	12645
B23:	LTTKAVLLVRKFQNS	12153
B24:	TTKAVLLVRKFQNS	7014
B25:	TKAVLLVRKFQNS	5753
B26:	TKAVLLVRKFQNS	5226
B27:	KAVLLVRKFQNS	5604
B28:	AVLLVRKFQNS	9073

B29:	VLLVRKFQNS	9099
B30:	LLVRKFQNS	7205
B31:	LVRKFQNS	2525
B32:	VRKFQNS	1182
B33:	PRSTPSLTTKAVLLVRKFQNS	11699
B34:	PRSTPSLTTKAVLLVRKFQN<u>A</u>	11450
B35:	PRSTPSLTTKAVLLVRKFQ<u>A</u>S	13185
B36:	PRSTPSLTTKAVLLVRKF<u>A</u>NS	10090
B37:	PRSTPSLTTKAVLLVRK<u>A</u>QNS	11556
B38:	PRSTPSLTTKAVLLVR<u>A</u>FQNS	11117
B39:	PRSTPSLTTKAVLLV<u>A</u>KFQNS	10786
B40:	PRSTPSLTTKAVLL<u>A</u>RKFQNS	4542
B41:	PRSTPSLTTK<u>AVLA</u>VRKFQNS	3758
B42:	PRSTPSLTTKAV<u>ALVRKFQNS</u>	3838
B43:	PRSTPSLTTKA<u>A</u>LLVRKFQNS	7157
B44:	PRSTPSLTT<u>A</u>AVLLVRKFQNS	19499
B45:	PRSTPSLT<u>A</u>KAVLLVRKFQNS	7487
B46:	PRSTPSL<u>A</u>TKAVLLVRKFQNS	7685
B47:	PRSTPS<u>A</u>TTKAVLLVRKFQNS	8566

These data indicate that the sequence VLLV is a critical binding region within domain II, that domain II is preferably flanked on the amino-terminus by an amino acid sequence R^{11}-X-, wherein R^{11} is a synthetic or naturally-occurring amino acid residue that is neutral or acidic under physiological conditions and X is any amino acid residue. More preferably, the sequence includes LTTR^{11}XVLLV, wherein X can optionally be alaninyl. Additionally, these data indicate that the sequence VLLV is preferably flanked on the carboxyl-terminus by a pharmaceutically acceptable substituent equivalent in size to 1 to 3 amino acid residues, or more preferably, by 4 to 6 amino acid residues.

Example 3

This example provides data identifying the critical binding regions of domain III, as well as which residues

within the critical binding domain are essential and/or important in the binding of human IL-6 ligand to IL-6 receptor within domain III.

Peptide Identifier	Peptide Sequence	Counts/minute bound
C1:	SSFYRLRFELRYRAERSKTFT	14571
C2:	SSFYRLRFELRYRAERSKTF	13763
C3:	SSFYRLRFELRYRAERSKT	8210
C4:	SSFYRLRFELRYRAERSK	7619
C5:	SSFYRLRFELRYRAERS	4707
C6:	SSFYRLRFELRYRAER	2653
C7:	SSFYRLRFELRYRAE	1821
C8:	SSFYRLRFELRYRA	2509
C9:	SSFYRLRFELRYR	2173
C10:	SSFYRLRFELRY	1354
C11:	SSFYRLRFELR	1127
C12:	SSFYRLRFEL	1031
C13:	SSFYRLRFE	1019
C14:	SSFYRLRF	952
C15:	SSFYRLR	991
C16:	SSFYRL	865
C17:	SSFYRLRFELRYRAERSKTFT	15127
C18:	SFYRLRFELRYRAERSKTFT	12750
C19:	FYRLRFELRYRAERSKTFT	10136
C20:	YRLRFELRYRAERSKTFT	7574
C21:	RLRFELRYRAERSKTFT	5991
C22:	LRFELRYRAERSKTFT	9610
C23:	RFELRYRAERSKTFT	5307
C24:	FELRYRAERSKTFT	5113
C25:	ELRYRAERSKTFT	2204
C26:	LRYRAERSKTFT	6382
C27:	RYRAERSKTFT	3150
C28:	YRAERSKTFT	2401
C29:	RAERSKTFT	1432
C30:	AERSKTFT	1202
C31:	ERSKTFT	1033
C32:	RSKTFT	1345
C33:	SSFYRLRFELRYRAERSKTFT	14610
C34:	SSFYRLRFELRYRAERSKTF**A**	16952
C35:	SSFYRLRFELRYRAERSKT**A**T	14809
C36:	SSFYRLRFELRYRAERSK**A**FT	15011
C37:	SSFYRLRFELRYRAERS**A**TFT	7223
C38:	SSFYRLRFELRYRAER**A**KTFT	12308

C39:	SSFYRLRFELRYRAEASKTFT	3430
C40:	SSFYRLRFELRYRAARSKTFT	17299
C41:	SSFYRLRFELRY*AAERSKTFT*	6743
C42:	SSFYRLRFELRARAERSKTFT	17461
C43:	SSFYRLRFELAYRAERSKTFT	7548
C44:	SSFYRLRFEARYRAERSKTFT	14120
C45:	SSFYRLRFALRYRAERSKTFT	26802
C46:	SSFYRLRAELRYRAERSKTFT	13395
C47:	SSFYRLAFELRYRAERSKTFT	9762

These data indicate that the sequence LRYRAERS is a critical binding region within domain III, that domain III is preferably flanked on the amino-terminus by an amino acid residue R^{21}, wherein R^{21} is a synthetic or naturally-occurring amino acid residue that has a side-chain that is neutral or basic under physiological conditions. Additionally, these data show that any of the amino acid residues of the critical binding domain can be replaced, preferably by a conservative substitution, and that the argininyl residues of the critical binding region are most important to the binding of the peptide. Moreover, while not meaning to be bound by any particular theory, it is apparent that this region of the protein exists in a pleated-sheet motif. Accordingly, substitutions of amino acid residues by structure-breaking amino acid residues, e.g., prolinyl, is less preferred.

Example 4

This example provides data identifying the critical binding regions of domain IV, as well as which residues within the critical binding domain are essential and/or important in the binding of human IL-6 ligand to IL-6 receptor within domain IV. In the following tabulation

of data, rows D1-D10 were examined in one experiment, and rows D11-D57 were examined in a separate experiment. Thus, the numerical data obtained from rows D1-D10 should not be directly compared to the numerical data from rows D11-D57.

Peptide Identifier	Peptide Sequence	Counts/minute bound
D1:	ATSLPVQDSSSVPLPTFLVAG	3995
D2:	VQDSSSVPLPTFLVAGGSLAF	4521
D3:	SVPLPTFLVAGGSLAFGTLLC	19756
D4:	TFLVAGGSLAFGTLLCIAIVL	32022
D5:	GGSLAFGTLLCIAIVLRFKKT	159174
D6:	FGTLLCIAIVLRFKKTWKLRA	143540
D7:	CIAIVLRFKKTWKLRALKEGK	52538
D8:	LRFKKTWKLRALKEGKTSMHP	20399
D9:	TWKLRALKEGKTSMHPPYSLG	5530
D10:	ALKEGKTSMHPPYSLGQLVPE	4969
D11:	GGSLAFGTLLCIAIVLRFKKT	20349
D12:	GGSLAFGTLLCIAIVLRFKK	18081
D13:	GGSLAFGTLLCIAIVLRFK	16082
D14:	GGSLAFGTLLCIAIVLRF	7694
D15:	GGSLAFGTLLCIAIVLR	3948
D16:	GGSLAFGTLLCIAIVL	2456
D17:	GGSLAFGTLLCIAIV	1344
D18:	GGSLAFGTLLCIAI	1175
D19:	GGSLAFGTLLCIA	1153
D20:	GGSLAFGTLLCI	1202
D21:	GGSLAFGTLLC	1108
D22:	GGSLAFGTLL	1001
D23:	GGSLAFGTL	997
D24:	GGSLAFGT	981
D25:	GGSLAFG	952
D26:	GGSLAF	1047
D27:	GGSLAFGTLLCIAIVLRFKKT	21945
D28:	GSLAFGTLLCIAIVLRFKKT	26441
D29:	SLAFGTLLCIAIVLRFKKT	24724
D30:	LAFGTLLCIAIVLRFKKT	22737
D31:	AFGTLLCIAIVLRFKKT	24047
D32:	FGTLLCIAIVLRFKKT	21799

D33:	GTLLCIAIVLRFKKT	15730
D34:	TLLCIAIVLRFKKT	12412
D35:	LLCIAIVLRFKKT	15510
D36:	LCIAIVLRFKKT	12422
D37:	CIAIVLRFKKT	8352
D38:	IAIVLRFKKT	6800
D39:	AIVLRFKKT	4879
D40:	IVLRFKKT	4452
D41:	VLRFKKT	2551
D42:	LRFKKT	1958
D43:	GGSLAFGTLLCIAIVLRFKKT	20385
D44:	GGSLAFGTLLCIAIVLRFKK<u>A</u>	21366
D45:	GGSLAFGTLLCIAIVLRFK<u>A</u>T	28625
D46:	GGSLAFGTLLCIAIVLRF<u>A</u>KT	30792
D47:	GGSLAFGTLLCIAIVLR<u>A</u>KKT	20934
D48:	GGSLAFGTLLCIAIVL<u>A</u>FKKT	29450
D49:	GGSLAFGTLLCIAIV<u>A</u>RFKKT	22065
D50:	GGSLAFGTLLCIAI<u>A</u>LRFKKT	17857
D51:	GGSLAFGTLL<u>CIAA</u>VLRFKKT	28461
D52:	GGSLAFGTLLC<u>A</u>AIVLRFKKT	27699
D53:	GGSLAFGTLL<u>A</u>IAIVLRFKKT	34879
D54:	GGSLAFGTL<u>A</u>CIAIVLRFKKT	22037
D55:	GGSLAFGT<u>A</u>LCIAIVLRFKKT	22123
D56:	GGSLAFG<u>A</u>LLCIAIVLRFKKT	22973
D57:	GGSLAF<u>A</u>TLLCIAIVLRFKKT	22324

These data indicate that the sequence IAIVLRF is a critical binding region within domain IV, that this critical binding domain is preferably flanked on the carboxyl-terminus by one or two lysinyl residues, or at least a pharmaceutically acceptable substituent comparable in size to one to three amino acid residues, which are -KKT in the sequence of the human IL-6 receptor. These data also show that the sequence is preferably flanked on the amino-terminus by a pharmaceutically acceptable substituent comparable in size to one, two, three, four, five, or six or more amino

acid residues. Of course, the pharmaceutically acceptable substituents could be synthetic or naturally-occurring amino acid residues. Moreover, the data show that any one of the amino acid residues can be replaced by an alaninyl residue, resulting in an increase in affinity for IL-6. One skilled in the art will also appreciate that multiple (e.g., two or three) substitutions can be made in the critical binding region, and that when multiple replacements or substitutions are made, then the substitutions are preferably conservatively selected. Additionally, the skilled artisan will note that the critical amino acid sequence IAIVLRF resides in an extended region that has high affinity for the IL-6 ligand and that four of the seven amino acid residues of this critical region can be found at either the amino- or carboxyl terminus of a polypeptide comprising the sequence.

Example 5

This example employs essentially the same techniques as Examples 1-4 except that fragments of the β-chain of the IL-6 receptor are used. As is known in the art, the β-chain is shared by multiple receptors. Thus, the identified fragments here are effective inhibitors of a multiplicity of binding reactions in addition to the IL-6 ligand:IL-6 receptor interaction.

Peptide Identifier	Peptide Sequence	Counts/minute bound
E1:	MLTLQTWVVQALFIFLTTESTGEL	3365
E2:	ALFIFLTTESTGELLDPCGYISPE	1531
E3:	TGELLDPCGYISPESPVVQLHSNF	1300
E4:	ISPESPVVQLHSNFTAVCVLKEKC	1499

E5:	HSNFTAVCVLKEKCMDYFHVNANY	1292
E6:	KEKCMDYFHVNANYIVWKTNHFTI	1443
E7:	NANYIVWKTNHFTIPKEQYTIINR	1327
E8:	HFTIPKEQYTIINRTASSVTFTDI	1143
E9:	IINRTASSVTFTDIASLNIQLTCN	1628
E10:	FTDIASLNIQLTCNILTFGQLEQN	3376
E11:	LTCNILTFGQLEQNVYGITIISGL	1816
E12:	LEQNVYGITIISGLPPEKPKNLSC	1669
E13:	ISGLPPEKPKNLSCIVNEGKKMRC	1202
E14:	NLSCIVNEGKKMRCEWDGGRETHL	1171
E15:	KMRCEWDGGRETHLETNFTLKSEW	1573
E16:	ETHLETNFTLKSEWATHKFADCKA	1035
E17:	KSEWATHKFADCKAKRDTPTSCTV	1409
E18:	DCKAKRDTPTSCTVDYSTVYFVNI	1548
E19:	SCTVDYSTVYFVNIEVWVEAENAL	3317
E20:	FVNIEVWVEAENALGKVTSDHINF	1413
E21:	ENALGKVTSDHINFDPVYKVKPNP	1122
E22:	HINFDPVYKVKPNPPHNLSVINSE	1728
E23:	KPNPPHNLSVINSEELSSILKLTW	1414
E24:	INSEELSSILKLTWTNPSIKSVII	1007
E25:	KLTWTNPSIKSVIILKYNIQYRTK	10331
E26:	SVIILKYNIQYRTKDASTWSQIPP	2832
E27:	YRTKDASTWSQIPPEDTASTRSSF	1162
E28:	QIPPEDTASTRSSFTVQDLKPFTE	1202
E29:	RSSFTVQDLKPFTEYVFRIRCMKE	1318
E30:	PFTEYVFRIRCMKEDGKGYWSDWS	1263
E31:	CMKEDGKGYWSDWSEEASGITYED	1732
E32:	SDWSEEASGITYEDRPSKAPSFWY	1161
E33:	TYEDRPSKAPSFWYKIDPSHTQGY	1215
E34:	SFWYKIDPSHTQGYRTVQLVWKTL	1145
E35:	TQGYRTVQLVWKTLPPFEANGKIL	1169
E36:	WKTLPPFEANGKILDYEVTLTRWK	1465
E37:	GKILDYEVTLTRWKSHLQNYTVNA	1791
E38:	TRWKSHLQNYTVNATKLTVNLTND	3652
E39:	TVNATKLTVNLTNDRYLATLTVRN	4360
E40:	LTNDRYLATLTVRNLVGKSDAAVL	4802
E41:	TVRNLVGKSDAAVLTIPACDFQAT	1104
E42:	AAVLTIPACDFQATHPVMDLKAFP	1121
E43:	FQATHPVMDLKAFPKDNMLWVEWT	1299
E44:	KAFPKDNMLWVEWTTPRESVKKYI	1175
E45:	VEWTTPRESVKKYILEWCVLSDKA	1389

E46:	KKYILEWCVLSDKAPCITDWQQED	1712
E47:	SDKAPCITDWQQEDGTVHRTYLRG	2079
E48:	QQEDGTVHRTYLRGNLAESKCYLI	1082
E49:	YLRGNLAESKCYLITVTPVYADGP	1541
E50:	CYLITVTPVYADGPGSPESIKAYL	1259
E51:	ADGPGSPESIKAYLKQAPPSKGPT	1194
E52:	KAYLKQAPPSKGPTVRTKKVGKNE	1816
E53:	KGPTVRTKKVGKNEAVLEWDQLPV	1636
E54:	GKNEAVLEWDQLPVDVQNGFIRNY	1307
E55:	QLPVDVQNGFIRNYTIFYRTIIGN	4355
E56:	IRNYTIFYRTIIGNETAVNVDSSH	1635
E57:	IIGNETAVNVDSSHTEYTLSSLTS	1232
E58:	DSSHTEYTLSSLTSDTLYMVRMAA	1353
E59:	SLTSDTLYMVRMAAYTDEGGKDGP	1270
E60:	RMAAYTDEGGKDGPEFTFTTPKFA	1447
E61:	KDGPEFTFTTPKFAQGEIEAIVVP	1393
E62:	PKFAQGEIEAIVVPVCLAFLLTTL	2794
E63:	IVVPVCLAFLLTTLLGVLFCFNKR	4519
E64:	LTTLLGVLFCFNKRDLIKKHIWPN	4501
E65:	FNKRDLIKKHIWPNVPDPSKSHIA	5741
E66:	IWPNVPDPSKSHIAQWSPHTPPRH	1203
E67:	SHIAQWSPHTPPRHNFNSKDQMYS	1199
E68:	PPRHNFNSKDQMYSDGNFTDVSVV	1231
E69:	QMYSDGNFTDVSVVEIEANDKKPF	1194
E70:	VSVVEIEANDKKPFPEDLKSLDLF	1305
E71:	KKPFPEDLKSLDLFKKEKINTEGH	2694
E72:	LDLFKKEKINTEGHSSGIGGSSCM	1443
E73:	TEGHSSGIGGSSCMSSSRPSISSS	1060
E74:	SSCMSSSRPSISSSDENESSQNTS	1131
E75:	ISSSDENESSQNTSSTVQYSTVVH	1118
E76:	QNTSSTVQYSTVVHSGYRHQVPSV	1197
E77:	TVVHSGYRHQVPSVQVFSRSESTQ	1247
E78:	VPSVQVFSRSESTQPLLDSEERPE	1229
E79:	ESTQPLLDSEERPEDLQLVDHVDG	1384
E80:	ERPEDLQLVDHVDGGDGILPRQQY	1214
E81:	HVDGGDGILPRQQYFKQNCSQHES	1097
E82:	RQQYFKQNCSQHESSPDISHFERS	1087
E83:	QHESSPDISHFERSKQVSSVNEED	1250
E84:	FERSKQVSSVNEEDFVRLKQQISD	1015
E85:	NEEDFVRLKQQISDHISQSCGSGQ	1113
E86:	QISDHISQSCGSGQMKMFQEVSAA	1239

E87:	GSGQMKMFQEVSAADAFGPGTEGQ	1001
E88:	VSAADAFGPGTEGQVERFETVGME	1091
E89:	TEGQVERFETVGMEAATDEGMPKS	1131
E90:	VGMEAATDEGMPKSYLPQTVRQGG	1385
E91:	MPKSYLPQTVRQGGYMPQ	1226

These data demonstrate that the sequence SVIILKYNIQY is sufficient to bind to IL-6 ligand; however, better binding can be obtained by a sequence comprising the sequence PSIKSVIILKYNIQY and the sequence can optionally comprise either WTNPSIKSVIILKYNIQY or even KLTWTNPSIKSVIILKYNIQY.

These data also indicate that the sequence TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL comprises a multiplicity of subsequences, each of which can bind with IL-6 ligand. Similarly, QLPVDVQNGFIRNYTIFYRTIIGN comprises a multiplicity of subsequences, each of which can bind with IL-6 ligand. Additionally, the sequence IVVPVCLAFLLTTLLGVLFCFNKRDLIKKHIWPNVPDPSKSHIA comprises a multiplicity of subsequences, each of which can bind with IL-6 ligand.

For example, one skilled in the art will appreciate that any segment of the foregoing sequences comprising about six, twelve, eighteen, or twenty-four amino acid residues is expected to bind with IL-6 ligand. Moreover, these data indicate to the skilled artisan that a multiplicity of amino acid substitutions, particularly conservative amino acid substitutions, within any of the above-described polypeptides can yield additional polypeptides having a substantial ability to bind with IL-6 ligand and to inhibit the binding of IL-6 ligand to

IL-6 receptor and thereby inhibit IL-6 signaling under physiological conditions.

All publications cited herein are hereby incorporated by reference to the same extent as if each publication were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations of the preferred polypeptides, nucleic acids, compositions and methods, and the like can be used and that it is intended that the invention can be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

WHAT IS CLAIMED IS:

1. A polypeptide, which inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions and has the formula $R^1R^*R^*L^*L^*L^*R^*R^2$, and pharmaceutically acceptable salts thereof, wherein

R^1 does not comprise an amino acid residue sequence that is identical to an amino acid residue sequence of the α-chain of the IL-6 receptor and is not linked to the moiety $-R^*R^*L^*L^*L^*R^*$ via a glycinyl residue or via a proprionyl residue and is selected from the group consisting of hydrogen, $R^3C(O)-$, and R^3;

R^* is independently selected from the group consisting of argininyl, naturally-occurring argininyl equivalents, and synthetic argininyl equivalents;

L^* is independently selected from the group consisting of leucinyl, naturally-occurring leucinyl equivalents, and synthetic leucinyl equivalents;

R^2 is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, $-NHR^3$, and R^3; and

R^3 is a pharmaceutically acceptable substituent group.

2. The polypeptide of claim 1, wherein

R^* is independently selected from the group consisting of argininyl and lysinyl.

3. The polypeptide of claim 1, wherein

R^* is argininyl.

4. The polypeptide of any of claims 1-3, wherein L* is independently selected from the group consisting of leucinyl, isoleucinyl, and valinyl.

5. The polypeptide of any of claims 1-3, wherein L* is leucinyl.

6. The polypeptide of any of claims 1-5, wherein R^3 is R^4, and

R^4 is independently selected from the group consisting of a C_1-C_{18} alkyl, a C_2-C_{18} alkenyl, a C_2-C_{18} alkynyl, a C_6-C_{18} aryl, a C_7-C_{18} alkaryl, a C_7-C_{18} aralkyl, and a C_3-C_{18} cycloalkyl, wherein any of the foregoing R^3 groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur,

any of the foregoing R^4 groups can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C_1-C_8 monoalkylamine moiety, a C_1-C_8 dialkylamine moiety, and a C_1-C_8 trialkylamine moiety.

7. The polypeptide of claim 1, wherein said polypeptide is RRLLLR, wherein R is argininyl and L is leucinyl.

8. The polypeptide of any of claims 1-6, wherein R^2 is a -(serinyl-valinyl-R^5), and R^5 is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 98 amino acid residues, -NHR^4, and R^4, and

R^4 is independently selected from the group consisting of a C_1-C_{18} alkyl, a C_2-C_{18} alkenyl, a C_2-C_{18} alkynyl, a C_6-C_{18} aryl, a C_7-C_{18} alkaryl, a C_7-C_{18} aralkyl, and a C_3-C_{18} cycloalkyl, wherein any of the foregoing R^3 groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur,

any of the foregoing R^4 groups can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C_1-C_8 monoalkylamine moiety, a C_1-C_8 dialkylamine moiety, and a C_1-C_8 trialkylamine moiety.

9. A polypeptide, which inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions and has the formula $R^{10}R^{11}XVL^{*2}L^{*2}VR^{12}$, and pharmaceutically acceptable salts thereof, wherein

R^{10} is a pharmaceutically acceptable substituent;

R^{11} is selected from the group consisting of synthetic and naturally-occurring amino acid residues having an acidic or neutral side-chain under physiological conditions;

X is any synthetic or naturally-occurring amino acid residue;

V is valinyl;

L^{*2} is leucinyl or isoleucinyl; and

R^{12} is a pharmaceutically acceptable substituent.

10. A polypeptide of claim 9, wherein X is selected from the group consisting of synthetic and naturally-occurring amino acid residues that have an acidic or neutral side-chain under physiological conditions.

11. A polypeptide of claim 9 or 10, wherein L^{*2} is leucinyl.

12. A polypeptide of any of claims 9-11, wherein R^{12} is R^{13}-R^{14};

R^{13} is selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is acidic or neutral under physiological conditions; and

R^{14} is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, $-NHR^{15}$, and R^{15}; and

R^{15} is a pharmaceutically acceptable substituent group.

13. The polypeptide of any of claims 9-12, wherein

R^{13} is selected from the group consisting of naturally-occurring amino acid residues having a side-chain that is acidic or neutral under physiological conditions.

14. The polypeptide of any of claims 9-13, wherein

R^{13} is selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain consisting of a C_1-C_6 straight-chain or branched alkyl moiety.

15. The polypeptide of claim 12, wherein R^{13} is alaninyl.

16. The polypeptide of any of claims 9-15, wherein R^{15} is R^{16}, and

R^{16} is selected from the group consisting of hydrogen, a C_1-C_{18} alkyl, a C_2-C_{18} alkenyl, a C_2-C_{18} alkynyl, a C_6-C_{18} aryl, a C_7-C_{18} alkaryl, a C_7-C_{18} aralkyl, and a C_3-C_{18} cycloalkyl, wherein any of the foregoing R^{16} groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur, and

any of the foregoing R^{16} groups can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C_1-C_8 monoalkylamine moiety, a C_1-C_8 dialkylamine moiety, and a C_1-C_8 trialkylamine moiety.

17. The polypeptide of any of claims 9-16, wherein R^{10} is selected from the group consisting of hydrogen, a polypeptide of from 1 to about 100 amino acid residues, $R^{17}C(O)-$, and R^{17}; and

R^{17} is a pharmaceutically acceptable substituent group.

18. The polypeptide of claim 17, wherein R^{17} is selected from the group consisting of hydrogen, a C_1-C_{18} alkyl, a C_2-C_{18} alkenyl, a C_2-C_{18} alkynyl, a C_6-C_{18} aryl, a C_7-C_{18} alkaryl, a C_7-C_{18} aralkyl, and a C_3-C_{18} cycloalkyl, wherein any of the foregoing R^{17} groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur, and

any of the foregoing R^{17} groups can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C_1-C_8 monoalkylamine moiety, a C_1-C_8 dialkylamine moiety, and a C_1-C_8 trialkylamine moiety.

19. The polypeptide of claim 17, wherein R^{17} is hydrogen.

20. A polypeptide that inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions having the formula $R^{20}R^{21}L^{*}R^{*}Y^{*}R^{*}A^{*}E^{*}R^{*}S^{*}R^{22}$, wherein

R^{20} and R^{22} are pharmaceutically acceptable substituents;

R^{21} is selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is neutral or basic under physiological conditions;

L^{*}, Y^{*}, E^{*}, and S^{*} are each independently selected from the group consisting of synthetic or naturally-occurring amino acid residues;

R^{*} is independently selected from the group consisting of synthetic or naturally-occurring amino acid residues having a side-chain that is basic under physiological conditions; and

A^{*} is selected from the group consisting of alaninyl, glycinyl, isoleucinyl, leucinyl, valinyl, norleucinyl, norvalinyl, sarcosinyl, β-alaninyl, and α-aminoisobutyryl.

21. The polypeptide of claim 20, wherein R^{20} is selected from the group consisting of a polypeptide of from 1 to about 100 amino acid residues, hydrogen, $R^{23}C(O)-$, and R^{23}; and wherein

R^{23} is selected from the group consisting of a C_1-C_{18} alkyl, a C_2-C_{18} alkenyl, a C_2-C_{18} alkynyl, a C_6-C_{18} aryl, a C_7-C_{18} alkaryl, a C_7-C_{18} aralkyl, a C_3-C_{18} cycloalkyl, wherein any of the foregoing R^{23} groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which

can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur and

any of the foregoing R^{23} groups can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a C_1-C_8 monoalkylamine moiety, a C_1-C_8 dialkylamine moiety, and a C_1-C_8 trialkylamine moiety.

22. The polypeptide of claim 20 or 21, wherein R^{22} is selected from the group consisting of a polypeptide of from 1 to about 100 amino acid residues, hydrogen, $-NHR^{23}$, and R^{23}; and wherein

R^{23} is selected from the group consisting of a C_1-C_{18} alkyl, a C_2-C_{18} alkenyl, a C_2-C_{18} alkynyl, a C_6-C_{18} aryl, a C_7-C_{18} alkaryl, a C_7-C_{18} aralkyl, a C_3-C_{18} cycloalkyl, wherein any of the foregoing R^{23} groups that are cyclic comprise from 0 to 2 atoms per carbocyclic ring, which can be the same or different, selected from the group consisting of nitrogen, oxygen, and sulfur, and

any of the foregoing R^{23} groups can be substituted by one to about six substituents, which can be the same or different, selected from the group consisting of an amino moiety, a carbamate moiety, a carbonate moiety, a phosphamate moiety, a phosphate moiety, a phosphonate moiety, a pyrophosphate moiety, a triphosphate moiety, a sulfamate moiety, a sulfate moiety, a sulfonate moiety, a

C_1-C_8 monoalkylamine moiety, a C_1-C_8 dialkylamine moiety, and a C_1-C_8 trialkylamine moiety.

23. The polypeptide of any of claims 20-22, wherein R^{21} is alaninyl.

24. The polypeptide of any of claims 20-23, wherein R^* is argininyl.

25. The polypeptide of any of claims 20-24, wherein L^* is isoleucinyl or leucinyl.

26. The polypeptide of claim 25, wherein L^* is leucinyl.

27. The polypeptide of any of claims 20-26, wherein Y^* is selected from the group consisting of tyrosinyl, phenylalaninyl, tryptophanyl, and α-aminoisobutyryl.

28. The polypeptide of any of claims 20-27, wherein Y^* is tyrosinyl.

29. The polypeptide of any of claims 20-28, wherein E^* is selected from the group consisting of synthetic and naturally-occurring amino acid residues having an acidic side-chain under physiological conditions.

30. The polypeptide of claim 29, wherein E^* is selected from the group consisting of glutamyl, aspartyl, and γ-aminopentane-1,5-dioyl.

31. The polypeptide of claim 30, wherein E* is glutamyl.

32. The polypeptide of any of claims 20-31, wherein A* is alaninyl, glycinyl, or valinyl.

33. The polypeptide of claim 32, wherein A* is alaninyl.

34. The polypeptide of any of claims 20-33, wherein S* is selected from the group consisting of serinyl, threoninyl, phosphoserinyl, and phosphothreoninyl.

35. The polypeptide of claim 34, wherein S* is serinyl.

36. A polypeptide, which comprises a sequence that inhibits binding of IL-6 ligand with IL-6 receptor under physiological conditions, wherein said sequence comprises at least I*A*I*V*L*R*F*,

wherein I*, L*, and V* are independently selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain consisting of a C_1-C_6 straight-chain or branched alkyl moiety;

R* is independently selected from the group consisting of synthetic and naturally-occurring amino acid residues having a side-chain that is basic under physiological conditions;

A* is selected from the group consisting of alaninyl, glycinyl, isoleucinyl, leucinyl, valinyl, norleucinyl,

norvalinyl, sarcosinyl, β-alaninyl, and α-aminoisobutyryl;

F* is selected from the group consisting of tyrosinyl, phenylalaninyl, tryptophanyl, and α-aminoisobutyryl,

and wherein at least four of the seven substituents of I*A*I*V*L*R*F* are selected such that I* is isoleucinyl, A* is alaninyl, V* is valinyl, L* is leucinyl, R* is argininyl, and F* is phenylalaninyl;

and said polypeptide comprises less than about 200 contiguousamino acid residues that have a sequence that is identical to an amino acid sequence of the α-chain of the IL-6 receptor.

37. The polypeptide of claim 36, wherein said sequence comprises IAIVLRFK.

38. The polypeptide of claim 36, wherein said sequence comprises at least IAIVLRFKXX in which X is any synthetic or naturally-occurring amino acid residue.

39. The polypeptide of claim 36, wherein said sequence comprises at least LLCIAIVLRFK.

40. The polypeptide of claim 36, wherein said sequence comprises at least FGTLLCIAIVLRFKKT.

41. The polypeptide of any of claims 36-40, wherein said polypeptide has an amino acid residue sequence that is identical to the amino acid residue sequence of a span

of less than about 100 contiguous amino acid residues of the α-chain of the IL-6 receptor.

42. The polypeptide of claim 41, wherein said polypeptide has an amino acid residue sequence that is identical to the amino acid residue sequence of a span of less than about 30 contiguous amino acid residues of the α-chain of the IL-6 receptor.

43. The polypeptide of claim 42, wherein said polypeptide has an amino acid residue sequence that is identical to the amino acid residue sequence of a span of less than about 16 contiguous amino acid residues of the α-chain of the IL-6 receptor.

44. A polypeptide, which inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions, comprises up to about 200 contiguous amino acid residues that are identical to an amino acid residue sequence of the β-chain of the IL-6 receptor and comprises the sequence SVIILKYNIQY.

45. The polypeptide of claim 44, comprising the sequence PSIKSVIILKYNIQY.

46. The polypeptide of claim 44, comprising the sequence WTNPSIKSVIILKYNIQY.

47. The polypeptide of claim 44, comprising the sequence KLTWTNPSIKSVIILKYNIQY.

48. The polypeptide of any of claims 44-47, having up to about 100 contiguous amino acid residues that are identical to an amino acid residue sequence of the β-chain of the IL-6 receptor.

49. The polypeptide of any of claims 44-47, having up to about 50 contiguous amino acid residues that are identical to an amino acid residue sequence of the β-chain of the IL-6 receptor.

50. The polypeptide of any of claims 44-47 consisting of the recited sequence.

51. The polypeptide of any of claims 44-50 comprising from 1 to about 6 conservative or neutral substitutions, wherein any indicated amino acid residue can be substituted with a synthetic or naturally-occurring amino acid residue, and wherein the polypeptide inhibits the binding of human IL-6 ligand to human IL-6 receptor under physiological conditions.

52. A polypeptide, which inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions, comprises up to about 200 contiguous amino acid residues that are identical to an amino residue sequence of the β-chain of the IL-6 receptor, and comprises a portion of the sequence TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL.

53. The polypeptide of claim 52, wherein said portion is about a 6-mer.

54. The polypeptide of claim 52, wherein said portion is about a 12-mer.

55. The polypeptide of claim 52, wherein said portion is about an 18-mer.

56. The polypeptide of claim 52, wherein said portion is about a 24-mer.

57. The polypeptide of any of claims 52-56, having up to about 100 contiguous amino acid residues that have an identical sequence to an amino acid residue sequence of the β-chain of the IL-6 receptor.

58. The polypeptide of any of claims 52-57, having up to about 50 contiguous amino acid residues that have an identical sequence to an amino acid residue sequence of the β-chain of the IL-6 receptor.

59. The polypeptide of any of claims 52-58, wherein said portion comprises from 1 to about 6 conservative or neutral substitutions, wherein any indicated amino acid residue can be substituted with a synthetic or naturally-occurring amino acid residue.

60. The polypeptide of any of claims 53-59, further comprising a pharmaceutically acceptable substituent.

61. A polypeptide, which inhibits the binding of IL-6 ligand with IL-6 receptor under physiological

conditions, comprises up to about 200 contiguous amino acid residues that are identical to an amino acid residue sequence of the β-chain of the IL-6 receptor, and comprises a portion of the sequence QLPVDVQNGFIRNYTIFYRTIIGN.

62. The polypeptide of claim 61, wherein said portion is about a 6-mer.

63. The polypeptide of claim 61, wherein said portion is about a 12-mer.

64. The polypeptide of claim 61, wherein said portion is about an 18-mer.

65. The polypeptide of any of claims 61-64, having up to about 100 contigous amino acid residues that have an identical sequence to an amino acid residue sequence of the β-chain of the IL-6 receptor.

66. The polypeptide of any of claims 61-65, having up to about 50 contiguous amino acid residues that have an identical sequence to an amino acid residue sequence of the β-chain of the IL-6 receptor.

67. The polypeptide of any of claims 61-66, wherein said portion comprises from 1 to about 6 conservative or neutral substitutions, wherein any indicated amino acid residue can be substituted with a synthetic or naturally-occurring amino acid residue.

68. The polypeptide of any of claims 61-67, further comprising a pharmaceutically acceptable substituent.

69. A polypeptide, which inhibits the binding of IL-6 ligand with IL-6 receptor under physiological conditions, comprises up to about 200 contiguous amino acid residues that are identical to an amino acid residue sequence of the β-chain of the IL-6 receptor, comprises a portion of the sequence IVVPVCLAFLLTTLLGVLFCFNKRDLIKKHIWPNVPDPSKSHIA.

70. The polypeptide of claim 69, wherein said portion is about a 6-mer.

71. The polypeptide of claim 69, wherein said portion is about a 12-mer.

72. The polypeptide of claim 69, wherein said portion is about an 18-mer.

73. The polypeptide of claim 69, wherein said portion is about a 24-mer.

74. The polypeptide of any of claims 69-73, having up to about 100 contiguous amino acid residues that have an identical sequence to an amino acid residue sequence of the β-chain of the IL-6 receptor.

75. The polypeptide of any of claims 69-73, having up to about 50 contiguous amino acid residues that have

an identical sequence to an amino acid residue sequence of the β-chain of the IL-6 receptor.

76. The polypeptide of any of claims 69-75, wherein said portion comprises from 1 to about 6 conservative or neutral substitutions, wherein any indicated amino acid residue can be substituted with a synthetic or naturally-occurring amino acid residue.

77. The polypeptide of any of claims 69-76, further comprising a pharmaceutically acceptable substituent.

78. The polypeptide of any of claims 1-77, wherein said polypeptide consists of naturally-occurring amino acid residues.

79. A nucleic acid that encodes the polypeptide of any of claims 1-78 and can be expressed in a cell.

80. The nucleic acid of claim 79, in which the nucleic acid encoding the polypeptide is operably linked to a signal sequence, wherein said signal sequence is translated as a fusion protein with the polypeptide to form a signal sequence-polypeptide fusion, and wherein said signal sequence can cause secretion of at least the polypeptide by a cell in which the nucleic acid is expressed.

81. A composition comprising the polypeptide of any of claims 1-78 or a nucleic acid of claim 79 or 80 and a carrier therefor.

82. The composition of claim 81, wherein said composition comprises an agent or substituent that increases the solubility of the polypeptide.

83. The composition of claim 82, wherein said agent that increases the solubility of the polypeptide is a liposome.

84. The composition of claim 82, wherein said substituent is a saccharide.

85. A composition comprising a solid support matrix to which is attached a polypeptide of any of claims 1-78 or an anti-antibody to a polypeptide sequence selected from the group consisting of RRLLLR, RXVLLV, LRYRAERS, IAIVLRF, SVIILKYNIQY, PSIKSVIILKYNIQY, or a portion of any of the following polypeptides: WTNPSIKSVIILKYNIQY, KLTWTNPSIKSVIILKYNIQY, TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL, QLPVDVQNGFIRNYTIFYRTIIGN, and IVVPVCLAFLLTTLLGVLFCFNKRDLIKKHIWPNVPDPSKSHIA.

86. A method of prophylactically or therapeutically inhibiting IL-6 signaling in a mammal in need thereof, which method comprises administering to a mammal in need thereof an IL-6 signaling inhibiting effective amount of a polypeptide of any of claims 1-78, a nucleic acid of claim 79 or 80, or an antibody to a polypeptide of any of claims 1-78.

87. A method of removing IL-6 ligand from a bodily fluid of a mammal, which method comprises extra-corporeally contacting said bodily fluid with a solid support to which is attached a polypeptide of any of claims 1-78 or an anti-antibody to a polypeptide sequence selected from the group consisting of RRLLLR, RXVLLV, LRYRAERS, IAIVLRF, SVIILKYNIQY, PSIKSVIILKYNIQY, or a portion of any of the following polypeptides: WTNPSIKSVIILKYNIQY, KLTWTNPSIKSVIILKYNIQY, TRWKSHLQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVL, QLPVDVQNGFIRNYTIFYRTIIGN, and IVVPVCLAFLLTTLLGVLFCFNKRDLIKKHIWPNVPDPSKSHIA.

		Formula	MW
E-2560	H-Val-OH	$C_5H_{11}NO_2$	117.15
E-3250	H-[^{15}N]Val-OH	$C_5H_{11}{}^{15}NO_2$	118.15
F-2180	H-D-Val-OH	$C_5H_{11}NO_2$	117.15
F-3025	H-DL-Val-OH	$C_5H_{11}NO_2$	117.15
E-3S10	H-Val-ally ester p-tosylate	$C_8H_{16}NO_2 \cdot C_7H_8O_3S$	330.43
E-2565	H-Val-NH_2 · HBr	$C_5H_{12}N_7O \cdot HBr$	197.08
E-2570	H-Val-NH_2 · HCl	$C_5H_{12}N_2O \cdot HCl$	152.63
E-2585	H-Val-NHtBu	$C_9H_{20}N_2O$	172.27
E-2600	H-Val-p-nitrobenzyl ester · HBr	$C_{12}H_{16}N_2O_4 \cdot HBr$	333.19
E-2590	H-Val-OtBu · HCl	$C_9H_{19}NO_2 \cdot HCl$	209.72
F-3170	H-D-Val-OtBu · HCl	$C_9H_{19}NO_2 \cdot HCl$	209.72
E-2575	H-Val-OBzL · HCl	$C_{12}H_{12}NO_2 \cdot HCl$	243.74
E-2580	H-Val-OBzL · p-tosylate	$C_{12}H_{17}NO_2 \cdot C_7H_8O_3S$	379.48
F-3500	H-D-Val-OBzL · p-tosylate	$C_{12}H_{17}NO_2 \cdot C_7H_8O_3S$	379.48
E-1825	H-Val-OEt · HCl	$C_7H_{15}NO_2 \cdot HCl$	181.65
E-2595	H-Val-OMe · HCl	$C_6H_{13}NO_2 \cdot HCl$	167.64
F-3160	H-D-Val-OMe · HCl	$C_6H_{13}NO_2 \cdot HCl$	167.64
C-3700	Z-N-Me-Val-OH	$C_{14}H_{19}NO_4$	265.31
C-2805	Z-Val-OH	$C_{13}H_{17}NO_4$	251.28
C-2810	Z-D-Val-OH	$C_{13}H_{17}NO_4$	251.28
C-2815	Z-Val-NHtBu	$C_{12}H_{26}N_2O_3$	306.41
C-2830	Z-Val-ONp	$C_{19}H_{20}N_2O_4$	372.38
C-2820	Z-Val-OSu	$C_{17}H_{20}N_2O_4$	348.36
C-2825	Z-D-Val-OSu	$C_{17}H_{20}N_2O_4$	348.36

Fig. 1

Special Amino Acids and Amino Acid Derivatives

F-1190	H-Abu-OH
F-2440	H-Abu-NH_2 · HCl
F-3035	H-Abu-OtBu · HCl
F-3755	H-γ-Abu-OtBu · HCl
E-2660	Ac-p-aminohippuric acid
F-1015	Ac-p-amino-Phe-OMe
F-2275	Ac-p-bromo-DL-Phe-OH
F-3265	Ac-p-Bz-D-Phe-OH [Ac-D-Bpa-OH]
M-1935	Ac-Cys(farnesyl)-OH
F-2930	Ac-Cys(farnesyl)-OMe
F-1020	Ac-Dob(Boc)-OH
F-3175	Ac-4,5 dehydro-Leu-OH
F-1030	Ac-3,5-dinitro-Tyr-OEt
F-1010	DL-2-Acetylamino-6-N-Boc-amino-4-hexynoic acid · DCHA
F-2295	Ac-p-fluoro-DL-Phe-OH
F-3015	Ac-p-iodo-D-Phe-OH
F-2940	Ac-Met(O)-OH
F-2305	Ac-5-Me-DL-Trp-OH
F-2420	Ac-D-2-Nal-OH
F-1080	Ac-DL-propargyl-Gly-OEt
E-3060	H-Aib-OtBu
F-1160	H-allo-Ile-OH
F-1165	H-D-allo-Ile-OH
F-1170	H-DL-allo-Ile-OH

F-1175	H-allo-Thr-OH
F-1180	H-D-allo-Thr-OH
F-2635	H-DL-allo-Thr-OH
F-2545	H-allo-Thr-OMe · HCl
F-2540	H-allo-Thr(tBu)-OH
F-2560	L-α-Aminoadipic acid [L-2-Aminohexanedioic acid]
F-2575	D-α –Aminoadipic acid [D-2-Aminohexanedioic acid]
F-1185	DL-α-Aminoadipic acid [DL-2-Aminohexanedioic acid]
F-3150	L-2-Aminoadipic acid-δ-2-butyl ester [L-2-Aminohexanedioic acid-δ-2-butyl ester
F-3130	L-α-Aminoadipic acid-δ-methyl ester · HCl [L-2-Aminohexanedioic acid-δ-methyl ester · HCl
F-3800	1-Aminocyclopropane-1-carbohydroxamic acid · HCl
F-3805	1-Aminocyclopropane-1-carboxylic acid
F-1200	H-4-Amino-3,5-diodo-Phe-OH
F-1205	7-Aminoheptanoic acid
F-3480	4-Amino-1-methylimidazole-2-carboxylic acid-ethyl ester · HCl
F-3485	4-Amino-1-methylpyrrole-2-carboxylic acid methyl ester · HCl
F-1225	H-p-Amino-Phe-OH · HCl
F-2855	H-p-Amino-D-Phe-OH · HCl
F-1230	H-p-Amino-DL-Phe-OH
F-1235	DL-α-Aminopimelic acid [DL-2-Aminoheptanedioic acid]
H-3605	4-Aminopiperidine-4-carboxylic acid [H-Pip-OH]
F-2740	L-2-Aminosuberic acid [L-2-Aminooctanedioic acid/H-Asu-OH]

F-3315	D-a-Aminosuberic acid [D-2-Aminooctanedioic acid/H-D-Asu-OH]
F-3305	DL-α-Aminosuberic acid [DL-2-Aminooctanedioic acid/H-DL-Asu-OH]
F3675	H-3-Amino-Tyr-OH • 2 HCl [5-Aminopentanoic acid-benzyl ester • p-tosylate]
E-1700	n-Aminovaleric acid-benzyl ester • p–tosylate [5-Aminopentanoic acid-benzyl ester • p-tosylate]
F-1281	L-Azetidine –2-carboxylic acid
F-2285	Azetidine-3-carboxylic acid
F3075	H-p-Azido-Phe-OH
F-2490	H-ß-(3-Benzothienyl)-Ala-OH
F-2485	H-ß-(3-Benzathienyl)-D-Ala-OH
F-1215	Bestatin [(2S,3R)-3Amino-2-hydroxy-4-phenylbutanoyl-L-leucine]
F-2630	S-[2,3-Bis(palmitoyloxy)-(2RS)-propyl]-N-palmitoyl-(R)-Cys-OH
A-1135	Boc-Abu-OH
A-1175	Boc-D-Abu-OH
A-1140	Boc-γ-Abu-OH
A-1145	Boc-Abu-ONp
A-3240	Boc-Abz-OH
A-2800	Boc-4-Abz-OH
A-4300	Boc-4-Abz-Osu
A2015	Boc-Aib-OH
A3825	Boc-Aib-Osu
A-3345	Boc-allo-Ile-OH
A-3735	Boc-D-allo-Ile-OH
A-1150	Boc-ε-aminocaproic acid
A-1155	Boc-ε-aminocaproic acid-Osu

A-1160	Boc-4-amino-3,5-diiodo-Phe-OH
A-1175	Boc-7-aminoheptanoic acid
A-1185	Boc-p-amino-Phe-OH
A-2980	Boc-p-amino-D-Phe-OH
A-3975	Boc-p-amino-Phe(Fmoc)-OH
A-4065	Boc-p-amino-D-Phe(Fmoc)-OH
A-1455	Boc-p-amino-Phe(Z)-OH
A-4370	1-Boc–4-aminopiperidine-4-carboxylic acid [H-Pip(Boc)-OH]
A-3310	Boc-11-aminoundecanoic acid
A-3405	Boc-ö-aminovaleric acid [Boc-5-aminopentanoic acid]
A-3S70	Boc-p-azido-Phe-OH
A-4200	Boc-p-azido-D-Phe-OH
A-3540	Boc-ß-(3-benzothienyl)-Ala-OH
A-3695	Boc-p-bromo-Phe-OH
A-4205	Boc-p-bromo-D-Phe-OH
A-4490	Boc-p-tBu-Phe-OH
A-4485	Boc-p-tBu-D-Phe-OH
A-3295	Boc-p-Bz-Phe-OH [Boc-Bpa-OH]
A-3S60	Boc-p-Bz-D-Phe-OH [Boc-D-Bpa-OH]
A-4325	Boc-p-carboxy-Phe(OtBu)-OH • DCHA
A-3860	Boc-ß-chloro-Ala-OH
A-1525	Boc-p-chloro-Phe-OH
A-2655	Boc-p-chloro-D-Phe-OH
A-1535	Boc-ß-cyano-Ala-OH

A-1540	Boc-ß-cyano-D-Ala-OH
A-4375	Boc-p-cyano-Phe-OH
A-3760	Boc-ß-cyclohexyl-Ala-OH
A-3840	Boc-ß-cyclohexyl-D-Ala-OH
A-2960	Boc-ß-cyclohexyl-Ala-OH • DCHA
A-2920	Boc-ß-cyclohexyl-D-Ala-OH • DCHA
A-4465	Boc-cyclohexyl-Gly-OH
A-4470	Boc-cyclohexyl-D-Gly-OH
A-3340	N-Boc-cyclohexylstatine [N-Boc-(3S,4S)-4-amino-5-cyclohexyl-3-hydroxypentanoic acid]
A-4150	Boc-ß-cyclopropyl-Ala-OH
A-3215	Boc-Dab-OH
A-4215	Boc-D-Dab-OH
A-4415	Boc-Dab-OtBu • HCl
A-4125	Boc-Dab-(Aloc)-OH
A-3480	Boc-Dab-(Boc)-OH • DCHA
A-3S20	Boc-Dab-(Fmoc)-OH
A-4230	Boc-D-Dab(Fmoc)-OH
A-2905	Boc-Dab(Z)-OH • DCHA
A-4260	Boc-D-Dab(Z)-OH •DCHA
A-3220	Boc-Dap-OH
A-3S90	Boc-D-Dap-OH
A-4115	Boc-Dap(Aloc)-OH
A-3475	Boc-Dap(Boc)-OH • DCHA
A-4130	Boc-Dap(bromoacetyl)-OH
A-4290	Boc-Dap(Dnp)-OH
A-4295	Boc-Dap(Dnp)-OSu

A-3S80	Boc-Dap(Fmoc)-OH
A-4235	Boc-D-Dap(Fmoc)-OH
A-3000	Boc-Dap(Z)-OH · DCHA
A-4265	Boc-D-Dap(Z)-OH · DCHA
A-3485	Boc-4,5-dehydro-Leu-OH · DCHA
A-1550	Boc-3,4-dehydro-Pro-OH
A-1555	Boc-3,5-dibromo-Tyr-OH
A-4220	Boc-3,5-dibromo-D-Tyr-OH
A-4045	Boc-3,4-dichloro-D-Phe-OH
A-1580	Boc-3,5-diiodo-Tyr-OH
A-4225	Boc-3,5-diiodo-D-Tyr-OH
A-1590	Boc-3,5-diiodo-Tyr-OMe
A-1585	Boc-3,5-diiodo-Tyr-OSu
A-1410	Boc-3,5-diiodo-Tyr(3'-bromo-Bzl)-OH
A-2570	Boc-3,5-diiodo-Tyr(2',6'-dichloro-Bzl)-OH
A-3065	Boc-p-fluoro-Phe-OH
A-2835	Boc-p-fluoro-D-Phe-OH
A-1605	Boc-p-fluoro-DL-Phe-OH
A-4320	Boc-α-(Fmoc-amino)-Gly-OH [Fmoc-α-(Boc-amino) Gly-OH]
A-4040	Boc-Homoarg-OH · HCl
A-3775	Boc-Homoarg$(Et)_2$-OH
A-3780	Boc-D-Homarg$(Et)_2$-OH
A-3935	Boc-Homoarg(NO_2)-OH
A-3465	Boc-Homocit-OH
A-2870	Boc-D-Homocit-OH
A-3420	Boc-Homocys(Mbzl)-OH

A-4255	Boc-D-Homocys(Mbzl)-OH
A-3610	Boc-Homocys(Trt)-OH
A-1190	Boc-Homophe-OH
A-1195	Boc-D-Homophe-OH
A-2830	Boc-Homopro-OH
A-3125	Boc-D-Homopro-OH
A-4165	Boc-7-hydroxy-Tic-OH
A-4170	Boc-7-hydroxy-D-Tic-OH
A-1800	Boc-p-iodo-Phe-OH
A-3640	Boc-p-iodo-D-Phe-OH
A-1805	Boc-p-iodo-DL-Phe-OH
A-3815	Boc-isonipecotic acid [Boc-piperidine-4-carboxylic acid]
A-3715	Boc-N-Me-Abz-OH
A-2025	Boc-N-Me-allo-Ile-OH
A-3730	Boc-N-Me-D-allo-Ile-OH
A-2880	Boc-N-Me-p-chloro-D-Phe-OH
A-2070	Boc-N-Me-p-nitro-Phe-OH · DCHA
A-4495	Boc-p-Me-Phe-OH
A-4500	Boc-p-Me-D-Phe-OH
A-1965	Boc-Met(O)-OH
A-2885	Boc-Met(O_2)-OH
A-4145	Boc-α-Me-DL-Val-OH
A-3225	Boc-1-Nal-OH
A-4305	Boc-D-1-Nal-OH
A-2850	Boc-2-Nal-OH
A-2575	Boc-D-2-Nal-OH

A-3110	Boc-Neopentylgly-OH
A-4210	Boc-D-Neopentylgly-OH
A-2125	Boc-p-nitro-Phe-OH
A-2130	Boc-p-nitro-D-Phe-OH
A-3645	Boc-Oic-OH [Boc-L-octohydroindole-2-carboxylic acid]
A-2965	Boc-Pen(Acm)-OH
A-2970	Boc-D-Pen(Acm)-OH
A-3660	Boc-Pen(Mbzl)-OH · DCHA
A-3665	Boc-D-Pen(Mbzl)-OH · DCHA
A-2900	Boc-Pen(Mob)-OH
A-3990	Boc-D-Pen(Mob)-OH
A-3650	Boc-Pen(NPys)-OH
A-3655	Boc-D-Pen(NPys)-OH
A-3S50	Boc-Pen(Trt)-OH
A-3S55	Boc-D-Pen(Trt)-OH
A-3915	Boc-pentafluoro-Phe-OH
A-3960	Boc-pentafluoro-D-Phe-OH
A-4385	Boc-p-phenyl-Phe-OH [Boc-β-(4-biphenyl)-Ala-OH; Boc-Bip-OH]
A-4390	Boc-p-phenyl-D-Phe-OH [Boc-β-(4-biphenyl)-D-Ala-OH; Boc-D-Bip-OH]
A-4100	N-Boc-phenylstatine [N-Boc-(3S,4S)-4-amino-3-hydroxy-5-phenylpentanoic acid]
B-3115	1-Boc-piperidine-4-Fmoc-amino-4-carboxylic acid [Fmoc-Pip(Boc)-OH]
A-3745	Boc-β-(3-pyridyl)-Ala-OH
A-2855	Boc-β -(3-pyridyl)-D-Ala-OH
A-4395	Boc-β-(2-quinolyl)-Ala-OH
A-4400	Boc-β-(2-quinolyl)-D-Ala-OH

A-1180	N-Boc-statine [N-Boc-(3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid]
A-3945	Boc-L-thiazolidine-4-carboxylic acid [Boc-L-thioproline]
A-3940	Boc-D-thiazolidine-4-carboxylic acid [Boc-D-thioproline]
A-2290	Boc-β-(2-thienyl)-Ala-OH
A-2295	Boc-β-(2-thienyl)-D-Ala-OH
A-2300	Boc-β-(2-thienyl)-DL-Ala-OH
A-3700	Boc-L-thiocitrulline-OtBu
A-4360	Boc-Thionoala-1-(6-nitro)benzotriazolide
A-4345	Boc-Thionoleu-1-(6-nitro)benzotriazolide
A-4355	Boc-Thionophe-1-(6-nitro)benzotriazolide
A-4365	Boc-Thionoser(Bzl)-1-(6-nitro)benzotriazolide
A-4350	Boc-Thionoval-1-(6-nitro)benzolriazolide
A-3070	Boc-Tic-OH
A-3075	Boc-D-Tic-OH
A-4090	Boc-D-Tpi-OH [Boc-D-1,2,3,4-telrahydronoharman-3-carboxylic acid]
F-1305	H-p-Bromo-Phe-OH
F-3700	H-p-Bromo-D-Phe-OH
F-1310	H-p-Bromo-DL-Phe-OH
F-3790	H-p-tBu-Phe-OH
F-3795	H-p-tBu-D-Phe-OH
F-3250	n-Butyloxycarbonyl-Dap-OH
F-2800	H-p-Bz-Phe-OH [H-Bpa-OH]
F-2810	H-p-Bz-D-Phe-OH [H-D-Bpa-OH]

F-2345	Carbamoyl-DL-Ala-OH
F-1375	Carbamoyl-β-Ala-OH
M-2240	Carbamoyl-Asp-OH · magnesium salt
F-2430	Carbamoyl-Leu-OH
Q-1140	β-Carboline-3-carboxylic acid-ethyl ester
Q-1145	β-Carboline-3-carboxylic acid-propyl ester
F-3590	H-p-Carboxy-Phe-OH
F-3585	H-p-Carboxy-Phe(OtBu)-OH
F-2700	L-Carnitine [(R)-β-Hydroxy-γ-(trimethylammonio)butyrate]
F-1425	H-β-Chloro-Ala-OH
F-1430	H-β-Chloro-Ala-OH · HCl
F-1435	H-β-Chloro-D-Ala-OH · HCl
F-1440	H-β-Chloro-DL-Ala-OH
F-2325	H-β-Chloro-DL-Ala-OH · HCl
F-3380	H-β-Chloro-Ala-NHOH
F-3465	H-β-Chloro-Ala-OMe · HCl
F-1445	H-p-Chloro-Phe-OH
F-2520	H-p-Chloro-D-Phe-OH
F-1450	H-p-Chloro-DL-Phe-OH
F-2690	H-p-Cloro-D-Phe-OMe · HCl
F-1455	H-p-Chloro-DL-Phe-OMe · HCl
F-1460	H-β-Cyano-Ala-OH
F-3610	H-p-Cyano-Phe-OH
F-2500	H-β-Cyclohexyl-Ala-OH · HCl
F-2505	H-β-Cyclohexyl-D-Ala-OH · HCl
F-3760	H-Cyclohexyl-Gly-OH · salt
F-3765	H-Cyclohexyl-D-Gly-OH · salt

F-2830	Cyclohexylstatine [(3S,4S)-4-Amino-5-cyclohexyl-3-hydroxypentanoic acid]
F-1470	H-β-(1-Cyclopentenyl)-DL-Ala-OH
F-1465	H-β-(1-Cyclopentenyl)-DL-Ala-OH
F-3470	H-β-Cyclopropyl-Ala-OH
F-1475	L-Cycloserine
F-1480	D-Cycloserine
F-1485	DL-Cycloserine
F-3050	H-Dob-OH · 2 HCl
F-3055	H-D-Dob-OH · 2 HCl
A-3305	H-Dob(Boc)-OH
E-3360	H-Dob(Boc)-OMe · HCl
F-3040	H-Dop-OH · HCl
F-3045	H-D-Dop-OH · HCl
F-3420	H-Dop(Boc)-OMe · HCl
F-2985	H-4,5-Dehydro-Leu-OH
F-2970	H-trans-4,5-Dehydro-Lys-OH [DL-trans-2,6-Diamino-4-hexenoic acid]
F-1490	H-3,4 Dehydro-Pro-OH
F-2705	H-3,4-Dehydro-DL-Pro-OH
F-1495	H-3,4-Dehydro-Pro-NH_2 · HCl
F-1500	H-3,4-Dehydro-Pro-OMe · HCl
F-1505	2,6-Diaminopimelic (LL,DD and Meso) [2,6-Diaminoheptanedioic acid)
F-1510	H-6-Diazo-5-oxo-Nle-OH [L-DON]
F-2185	H-6-Diazo-5-oxo-D-Nle-OH [D-DON]

F-1520	H-3,5-Dibromo-Tyr-OH
F-3395	H-3,4-Dichloro-Phe-OH
F-3400	H-3,4-Dichloro-D-Phe-OH
F-3695	H-β,β, Dicyclohexyl-DL-Ala-OH
F-2395	H-α-Difluoro-Me-DL-Orn-OH [DFMO]
F-1525	H-β-(3,4-Dihydroxyphenyl)-DL-Ser-OH [DL-Threo-DOPS]
F-3460	H-2,5-Diiodo-His-OH · HCL
F-2225	H-3,5-Diiodo-Tyr-OH
F-3005	H-3,5-Diiodo-D-Tyr-OH
E-2385	H-3,5-Diiodo-Tyr-OMe · HCL
M-1925	FA-Cys(farnesyl)-OH
M-1920	FA-Cys(farnesyl)-OMe
F-2530	H-β-Fluoro-DL-Ala-OH
F-3285	H-m-Fluoro-Phe-OH
F-3290	H-m-Fluoro-D-Phe-OH
F-2135	H-m-Fluoro-DL-Phe-OH
F-1530	H-p-Fluoro-Phe-OH
F-2320	H-p-Fluoro-D-Phe-OH
F-1535	H-p-Fluoro-DL-Phe-OH
F-3820	H-p-Fluoro-Phe-OEt · HCL
F-3295	H-m-Fluoro-D-Phe-OMe · HCL
F-1540	H-p-Fluoro-DL-Phe-OMe · HCL
B-1780	Fmoc-Abu-OH
B-2920	Fmoc-D-Abu-OH
B-1910	Fmoc-γ-Abu-OH

B-3260	Fmoc-Abz-OH
B-2985	Fmoc-4-Abz-OH
B-1860	Fmoc-Aib-OH
B-2880	Fmoc-allo-Ile-OH
B-2230	Fmoc-D-allo-Ile-OH
B-3100	Fmoc-allo-Thr-OH
B-3090	Fmoc-D-allo-Thr-OH
B-1815	Fmoc-allo-Thr(tBu)-OH
B-1810	Fmoc-allo-Thr(tBu)-Odhbt
B-3280	Fmoc-α-allyl-DL-Gly-OH [Fmoc-DL-2-amino-4-pentanoic acid]
B-2440	Fmoc-L-α-aminoadipic acid-δ-t-butyl ester [Fmoc-L-2-aminohexanedioic acid-δ-t-butyl ester]
B-1560	Fmoc-ϵ-aminocoproic acid
B-3310	2-(Fmoc-amino)-3-(2,2-dimethyl-4H-benzol[1,3]dioxin-6-yl)-propionic acid
B-2070	Fmoc-p-amino-Phe-OH
B-1995	Fmoc-p-amino-Phe-(Boc)-OH
B-2930	Fmoc-p-amino-D-Phe-(Boc)-OH
B-2360	Fmoc-p-azido-Phe-OH
B-2830	Fmoc-ß-(3-benzothienyl)-Ala-OH
B-3320	Fmoc-p-tBu-Phe-OH
B-3325	Fmoc-p-tBu-D-Phe-OH
B-2220	Fmoc-p-Bz-Phe-OH [Fmoc-Bpa-OH]
B-2340	Fmoc-p-Bz-D-Phe-OH [Fmoc-D-Bpa-OH]
B-3070	Fmoc-p-carboxy-Phe(OtBu)-OH
B-2115	Fmoc-p-chloro-Phe-OH

B-1900	Fmoc-p-chloro-D-Phe-OH
B-3125	Fmoc-p-cyano-Phe-OH
B-1975	Fmoc-ß-cyclohexyl-Ala-OH
B-2345	Fmoc-ß-cyclohexyl-D-Ala-OH
B-3270	Fmoc-cyclohexyl-Gly-OH
B-3275	Fmoc-cyclohexyl-D-Gly-OH
B-2905	Fmoc-ß-cyclopropyl-Ala-OH
B-3120	Fmoc-Cys(Boc-3-aminopropyl)-OH
B-2300	Fmoc-Dab-OH
B-2365	Fmoc-D-Dab-OH
B-2860	Fmoc-Dab-(Adpoc)-OH
B-2850	Fmoc-Dab-(aloc)-OH
B-1800	Fmoc-Dab-(Boc)-OH
B-2960	Fmoc-D-Dab(Boc)-OH
B-2270	Fmoc-D-Dab(Fmoc)-OH
B-3250	Fmoc-Dab(Z)-OH
B-2385	Fmoc-Dap-OH
B-3055	Fmoc-D-Dap-OH
B-2865	Fmoc-Dap(Adpoc)-OH
B-2845	Fmoc-Dap(Aloc)-OH
B-2380	Fmoc-Dap(Boc)-OH
B-2965	Fmoc-D-Dap(Boc)-OH
B-2995	Fmoc-Dap(Dnp)-OH
B-2265	Fmoc-Dap(Fmoc)-OH
B-2255	Fmoc-4,5-dehydro-Leu-OH
B-1660	Fmoc-3,4-dehydro-Pro-OH

B-1275	Fmoc-3,5-dibromo-Tyr-OH
B-1285	Fmoc-3,5-Diiodo-Tyr-OH
B-3265	Fmoc-3,5,dinitro-Tyr-OH
B-2595	Fmoc-m-fluoro-Phe-OH
B-2835	Fmoc-p-fluoro-Phe-OH
B-3210	Fmoc-p-fluoro-D-Phe-OH
B-1550	Fmoc-p-fluoro-DL-Phe-OH
B-3130	Fmoc-Homoarg(Pmc)-OH
B-2250	Fmoc-Homocit-OH
B-2390	Fmoc-D-Homocit-OH
B-2405	Fmoc-Homocys(Trt)-OH
B-1535	Fmoc-Homophe-OH
B-2810	Fmoc-D-Homophe-OH
B-2285	Fmoc-Homopro-OH
B-2290	Fmoc-D-Homopro-OH
B-2750	Fmoc-p-iodo-Phe-OH
B-1740	Fmoc-3-iodo-Tyr-OH
B-3190	Fmoc-isonipecotic acid
B-2590	Fmoc-DL-Isoser-OH
B-3335	Fmoc-p-Me-Phe-OH
B-3330	Fmoc-p-Me-D-Phe-OH
B-2130	Fmoc-Met(O)-OH
B-1905	Fmoc-Met(O_2)-OH
B-1965	Fmoc-1-Nal-OH
B-3020	Fmoc-D-1-Nal-OH
B-2100	Fmoc-2-Nal-OH

B-1950	Fmoc-D-2-Nal-OH
B-2690	Fmoc-m-nitro-p-hydroxy-Phe-OH [Fmoc-m-nitro-Tyr-OH]
B-1395	Fmoc-p-nitro-Phe-OH
B-2350	Fmoc-p-nitro-D-Phe-OH
B-2690	Fmoc-m-nitro-Tyr-OH [Fmoc-m-nitro-p-hydroxy-Phe-OH]
B-2425	Fmoc-Oic-OH [Fmoc-L-actahydroindole-2-carboxylic acid]
B-1885	Fmoc-Pen(Acm)-OH
B-1915	Fmoc-D-Pen(Acm)-OH
B-1545	Fmoc-D-Pen(Bzl)-OH
B-2315	Fmoc-Pen-(Trt)-OH
B-2320	Fmoc-D-Pen(Trt)-OH
B-3155	Fmoc-p-phenyl-Phe-OH [Fmoc-ß-(4-biphenyl)-Ala-OH; Fmoc-Bip-OH]
B-3160	Fmoc-p-phenyl-D-Phe-OH [Fmoc-ß-(4-biphenyl)-D-Ala-OH; Fmoc-D-Bip-OH]
B-3195	1-Fmoc-piperidine-4-Fmoc-amino-4-carboxylic acid [Fmoc-Pip(Fmoc)-OH]
B-3175	Fmoc-4-piperidylacetic acid [Fmoc-4-carboxymethyl-piperidine]
B-2005	Fmoc-ß-(3-pyridyl)-Ala-OH
B-2040	Fmoc-ß-(3-pyridyl)-D-Ala-OH
B-3165	Fmoc-ß-(2-quinolyl)-Ala-OH
B-3170	Fmoc-ß-(2-quinolyl)-D-Ala-OH
B-1665	Fmoc-ß-(2-thienyl)-Ala-OH
B-2120	Fmoc-ß-(2-thienyl)-D-Ala-OH
B-1920	Fmoc-Tic-OH
B-1925	Fmoc-D-Tic-OH

B-2470	Fmoc-Tyr(PO_3H_2)-OH
B-1990	Fmoc-Tyr(PO_3Me_2)-OH
B-2275	Fmoc-D-Tyr(PO_3Me_2)-OH
E-2870	Glutaryl-Leu-OH · 2DCHA
G-4490	Hippuryl-Cys(2-aminoethyl)-OH [Bz-Gly-Cys(2-aminoethyl)-OH; BZ-Gly-4-thia-Lys-OH]
F-3815	H-α-Homoethyl-Gly-OH
F-2780	H-Homoarg-OH
F-2995	H-Homocit-OH
F-2735	H-D-Homocit-OH
F-1610	H-Homophe-OH
F-1615	H-D-Homophe-OH
F-1620	H-DL-Homophe-OH
F-1625	H-Homopro-OH
F-1630	H-D-Homopro-OH
F-2915	H-DL-Homopro-OH
F-2465	H-Homopro-OMe · HCl
F-3125	H-D-Homopro-OMe · HCl
F-3330	H-(2S,4S)-γ-Hydroxy-Glu-OH
F-3335	H-(2S,4R)-γ-Hydroxy-Glu-OH
Q-1420	o-Hydroxyhippuric acid [Salicyluric acid]
E-2655	p-Hydroxyhippuric acid
F-1650	H-DL-δ-Hydroxy-DL-Lys-OH · HCl
F-2335	H-DL-δ-Hydroxy-DL-Lys(Boc)-OH
F-3685	H-α-Hydroxy-nor-L-arginine [L-2-Amino-(4-2'-hydroxyguanidino) butyric acid]
F-2935	H-7-Hydroxy-Tic-OH

F-2990	H-7-Hydroxy-D-Tic-OH
F-1665	H-p-Iodo-Phe-OH
F-1670	H-p-Iodo-D-Phe-OH
F-1675	H-p-Iodo-DL-Phe-OH
F-3350	H-m-Iodo-Tyr-OH
F-1695	H-DL-Isoser-OH [H-DL-β-Amino-α-hydroxypropionic acid]
F-1195	Lysinoalanine·2 HCl (diastereomeric mixture: LL + LD) H-Lys(DL-2-amino-2-carboxyethyl)-OH · 2HCl
F-1765	N-Me-Aib-OH
F-1760	N-Me-allo-Ile-Obzl · P-tosylate
F-1795	H-α-Me-DL-His-OH · 2HCl
Q-1585	Melphalan-methyl esler · 2HCl [H-p-Dl(2-chloroethyl)amino-Phe-OMe · 2HCl]
F-1800	H-α-Me-DL-Leu-OH
F-1780	N-Me-p-nitro-Phe-OH
E-3150	H-α-Me-Phe-OH
F-3115	H-α-Me-D-Phe-OH
F-1805	H-α-Me-DL-Phe-OH
F-2805	H-α-Me-DL-Phe-OMe · HCl
F-3780	H-p-Me-Phe-OH
F-3785	H-p-Me-D-Phe-OH
F-3440	H-α-Me-Pro-OH
F-3615	H-2-Mercapto-His-OH
F-3620	H-2-Mercapto-His-OMe
M-2345	H-β-(7-Methoxycoumarin-4yl)-Ala-OH [L-2-Amino-3-(7-methoxycoumarin-4-yl)-propionic acid]
F-3810	1-Methylaminocyclopropone-1-carboxylic acid

F-1815	H-γ-Methylene-DL-Glu-OH
Q-1645	(2-Methyl-1-indolyl)acetic · DCHA
F-3180	S-Methyl-L-thiocitrulline · acetate
F-2945	H-Met(O)-OH
F-2895	H-Met(O_2)-OH
F-1810	H-α-Me-DL-Trp-OH
F-2240	H-α-Me-DL-Trp-OMe
F-1820	H-1-Me-DL-Trp-OH
F-3535	H-α-Me-Val-OH
F-3540	H-α-Me-D-Val-OH
F-3355	H-α-Me-DL-Val-OH
F-2550	Myristoyl-Gly-OH
F-1840	H-1-Nal-OH
F-1845	H-D-1-Nal-OH
F-1850	H-DL-1-Nal-OH
F-1855	H-2-Nal-OH
F-1860	H-D-2-Nal-OH
F-1865	H-DL-2-Nal-OH
F-3710	H-2-Nal-Obzl · salt
F-1315	H-Neopentylgly-OH
F-1320	H-D-Neopentylgly-OH
F-1325	H-DL-Neopentylgly-OH
F-3340	H-m-Nitro-p-hydroxy-Phe-OH [H-m-Nitro-Tyr-OH]
F-1895	H-p-Nitro-Phe-OH
F-1900	H-p-Nitro-D-Phe-OH
F-1905	H-p-Nitro-DL-Phe-OH

F-1910	H-p-Nitro-Phe-OMe · HCl
F-3340	H-m-Nitro-Tyr-OH [H-m-Nitro-p-hydroxy-Phe-OH]
F-3105	H-Oic-OH [L-Octahydroindole-2-carboxylic acid]
F-2515	H-Pan-OH
F-3065	H-Pan(Trt)-OH
F-3645	H-β-Phenyl-Phe-OH [H-β-(4-Biphenyl)-Ala-OH; H-Bip-OH
F-3650	H-p-Phenyl-D-Phe-OH [H-β-(4-Biphenyl)-D-Ala-OH; H-D-Bip-OH
F-2040	H-Propargyl-Gly-OH
F-2900	H-D-Propargyl-Gly-OH
F-2860	H-DL-Propargyl-Gly-OH
F-2075	H-Propargyl-Gly-OMe · HCl
F-2825	H-β-(2-Pyridyl)-Ala-OH
F-2790	H-β-(2-Pyridyl)-D-Ala-OH
F-2825	H-β-(2-Pyridyl)-DL-Ala-OH
F-3195	H-β-(3-Pyridyl)-Ala-OH
F-2640	H-β-(3-Pyridyl)-D-Ala-OH
F-3705	H-β-(3-Pyridyl)-DL-Ala-OH
F-3655	H-β-(2-Quinolyl)-Ala-OH
F-3660	H-β-(2-Quinolyl)-D-Ala-OH
F-2030	H-Ser(PO_3H_2)-OH
F-2035	H-D-Ser(PO_3H_2)-OH
F-3365	H-Ser(SO_3H)-OH
F-3370	H-D-Ser(SO_3H)-OH

F-1220	Statine [(3S,4S)-4-Amino-3-hydroxy-6-methylheptanoic acid]
F-3665	L-4,5,6,7-Tetrahydra-1H-imidazo(4,5-c)pyridine-6-carboxylic acid
Q-1535	L-Thiozoldin-2-one-4-carboxlic acid [L-2-Oxothiozolidine-4-carboxlic acid]
F-2955	H-β-(2-Thiozolyl)-DL-Ala-OH
F-2110	H-β-(2-Thienyl)-Ala-OH
F-2115	H-β-(2-Thienyl)-D-Ala-OH
N-1150	H-β-(2-Thienyl)-DL-Ala-OH
F-2120	H-β-(2-Thienyl)-DL-Ser-OH
N-1195	DL-Thiorphan [(DL-3-Mercapto-2-benzylproponoyl)-Gly-OH]
F-2460	L-Thyronine [H-p-(p-Hydroxypheonoxy)-Phe-OH]
F-2405	DL-Thyronine [H-p-(p-Hydroxyphenoxy)-DL-Phe-OH]
F-2580	H-Tic-OH
F-2585	H-D-Tic-OH
F-3310	H-D-Tic-OtBu · HCl
Q-1700	H-Tpi-OH [L-1,2,3,4-Tetrahydronorharman-3-carboxlic acid]
F-3225	H-β-(1,2,4-Triozol-1yl)-DL-Ala-OH
F-3670	H-β-(Ureido)-Ala-OH [H-β-((Aminocarbonyl)amino)-Ala-OH; L-Albizziine)
C-1260	Z-Abu-OH
C-3160	Z-γ-Abu-OH
C-1265	Z-Abu-OSu
C-3350	Z-3-Abz-OSu
C-3680	Z-Aib-OH

C-3390	Z-allo-Thr(tBu)-OH · DCHA
C-3385	Z-L-α-aminoadipic acid [Z-L-2-aminohexanedioic acid]
C-3790	Z-L-2-aminoadipic acid-δ-t-butyl ester · DCHA [Z-L-2-aminohexanedioic acid]-δ-t-butyl ester · DCHA]
C-1270	Z-ε -aminocaproic acid
C-3975	Z-p-carboxy-Phe(OtBu)-OH
C-3920	Z-β-cyclohexyl-D-Ala-OH · DCHA
C-3705	Z-Dob-OH
C-3770	Z-D-Dob-OH
C-3510	Z-Dob(Boc)-OH · DCHA
C-3765	Z-D-Dob-(Boc)-OH · DCHA
C-3690	Z-Dob(Z)-OH
C-3315	Z-Dop-OH
C-3755	Z-D-Dop-OH
C-3685	Z-Dop(Boc)-OH · DCHA
C-3760	Z-D-Dop(Boc)-OH
C-3695	Z-Dop(Z)-OH
C-1535	Z-dehydro-Ala-OH
C-1540	Z-dehydro-Ala-OMe
C-3525	Z-p-fluoro-Phe-OH
C-3965	Z—D-Homocit-OH [Z-α-amino-ε-uneidocaproic acid]
C-1275	Z-Homophe-OH
C-1280	Z-D-Homophe-OH
C-3010	Z-1-Nal-OH
C3950	Z-D-1-Nal-OH
C-3500	Z-2-Nal-OH

C-2255	Z-D-2-Nal-OH
C-2260	Z-Neopentylgly-OH • DCHA
C-2265	Z-D-Neopenlylgly-OH
C-4030	Z-p-phenyl—Phe-OH [Z-ß-(4-biphenyl)-Ala-OH; Z-Bip-OH]
C-4035	Z-p-phenyl-D-Phe-OH [Z-ß-(4-biphenyl)-D-Ala-OH;Z-D-Bip-OH]
C-3870	Z-D-Tic-OH

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(54) Title: POLYPEPTIDES, COMPRISING IL-6 LIGAND-BINDING RECEPTOR DOMAINS, AND RELATED NUCLEIC ACIDS, ANTIBODIES, COMPOSITIONS, AND METHODS OF USE

(57) Abstract: The present invention provides polypeptides, and pharmaceutically acceptable salt thereof, that inhibit the binding of IL-6 ligand with IL-6 receptor under physiological conditions, a nucleic acid that encodes such a polypeptide, an antibody that is specific to such a polypeptide, a composition comprising such a polypeptide, a method of prophylactically or therapeutically inhibiting IL-6 signaling in a mammal in need thereof, and a method of removing IL-6 ligand from a bodily fluid of an animal.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 86 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 86

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Information on patent family members

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